

F. . ENT COOPERATION TREA .

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 18 January 2001 (18.01.01)	
International application No. PCT/US00/10784	Applicant's or agent's file reference 57743-A-PCT
International filing date (day/month/year) 21 April 2000 (21.04.00)	Priority date (day/month/year) 22 April 1999 (22.04.99)
Applicant MARZABADI, Mohammad, R. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 22 November 2000 (22.11.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Maria Kirchner Telephone No.: (41-22) 338.83.38
--	---

JPW

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
JOHN P. WHITE
COOPER & DUNHAM LLP
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

RECEIVED
COOPER & DUNHAM

JUN 27 2001

DOCKET CLERK

PCT

**NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

(PCT Rule 71.1)

Date of Mailing
(day/month/year)

Applicant's or agent's file reference

IMPORTANT NOTIFICATION

57743-A-PCT

International application No.

International filing date (day/month/year)

Priority date (day/month/year)

PCT/US00/10784

21 April 2000 (21.04.2000)

22 April 1999 (22.04.1999) ✓

Applicant

SYNAPTIC PHARMACEUTICAL CORPORATION

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

10.22.01 AP

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Form PCT/IPEA/416 (July 1992)

Authorized officer

Venkataraman Balasubramanian

Telephone No. (703)308-1235

TENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

T :
JOHN P. WHITE
COOPER & DUNHAM LLP
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

PCT NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing
(day/month/year)

25 JUN 2001

Applicant's or agent's file reference

57743-A-PCT

IMPORTANT NOTIFICATION

International application No.

PCT/US00/10784

International filing date (day/month/year)

21 April 2000 (21.04.2000)

Priority date (day/month/year)

22 April 1999 (22.04.1999)

Applicant

SYNAPTIC PHARMACEUTICAL CORPORATION

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Verkataraman Balasubramanian

Telephone No. (703)308-1235

Form PCT/IPEA/416 (July 1992)

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 57743-A-PCT		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/10784	International filing date (day/month/year) 21 April 2000 (21.04.2000)	Priority date (day/month/year) 22 April 1999 (22.04.1999)	
International Patent Classification (IPC) or national classification and IPC IPC(7): C07D 251/70, 277/28, 513/04; A61K 31/427, 31/429, 31/53; A61P 3/04; 7/04, 9/12. and US Cl.: 544/198, 209, 548/151, 190, 193, 194; 514/245, 366.			
Applicant SYNAPTIC PHARMACEUTICAL CORPORATION			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>7</u> sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of <u> </u> sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input checked="" type="checkbox"/> Non-establishment of report with regard to novelty, inventive step and industrial applicability</p> <p>IV <input checked="" type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p>			
Date of submission of the demand 22 November 2000 (22.11.2000)		Date of completion of this report 05 June 2001 (05.06.2001)	
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile N . (703)305-3230		Authorized officer <i>for</i> Venkataraman Balasubramanian Telephone No. (703)308-1235	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International Application No.

PCT/US00/10784

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed.

☒ the description:

pages 1-238 as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of _____

☒ the claims:

pages 239-280 as originally filed

pages NONE, as amended (together with any statement) under Article 19

pages NONE, filed with the demand

pages NONE, filed with the letter of _____

☒ the drawings:

pages 1-6 as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of _____

☐ the sequence listing part of the description:

pages NONE as originally filed

pages NONE, filed with the demand

pages NONE, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International Application No.

PCT/US00/10784

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 16 and 33-55 (in-part)

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 16 and 33-55 (in-part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/10784

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☒ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention is accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-15 and 43-55, drawn to triazine compounds and pharmaceutical composition where the core ring is triazine.

Group II, claim(s) 16-32, and 43-55 drawn to compound of claim 16 and pharmaceutical composition where Y= S.

Group III, claim(s) 33-55, drawn to compound of claim 33 and pharmaceutical composition where B= S.

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 1-55(in part)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International Application No.
PCT/US00/10784

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

V. 2. Citations and Explanations:

Claims 13-42 and 54-54 meet the criteria set out in PCT Article 33(2), because the prior art does not teach or fairly suggest the triazines or thiazole compound and method of use of the compound embraced in these claims.

Claims 1-12 and 43-53 lack novelty under PCT Article 33(2) as being anticipated by WO 99 05138 A1 (ZENYAKU KOGYO KABUSHIKI KAISHA). WO 99 05138 teaches several heterocycle substituted 1,3,5-triazines as antitumor agents which include compounds generically claimed herein. See formula (I) on page 1 abstract and note the definition of R₁-R₆. Note when R₃= piperazino or substituted piperidino group, reference compounds include those claimed herein. WO 99 05138 also teaches specifically substituted morpholine in the 4-position of triazine which would lead to the racemate of the instant optical isomers claimed herein. In absence of a purity limitation, the instantly claimed isomers read on the racemic mixture.

Claims 1-12 and 43-53 lack novelty under PCT Article 33(2) as being anticipated by EP 0 775 487 A1 (NIPPON SHINYAKU KOGYO). EP 0 775 487 teaches 2-amino-4- (2,5-dichlorophenyl)-6-substituted amino-1,3,5-triazine generically claimed herein for the use as hepatitis remedy. See formula I on page 3 and the definition of R₁ and R₂ groups. Note the -N (R₁ R₂) group as defined includes a number of R₈ groups embraced herein. See page 4 for the process of making these compounds and for experimental details and compounds made see page 6-24. Note compounds made include a sub genus of those claimed herein. EP 0 775 487 also teaches specifically 1 to 4 substituents in the cyclic amino group, namely -N (R₁ R₂) group substituted in the 4-position of triazine which would lead to the racemate of the instant optical isomers claimed herein. See formula (I) and page 4, line 10-19. In absence of a purity limitation, the instantly claimed isomers read on the racemic mixture.

Claims 1-12 and 43-53 lack novelty under PCT Article 33(2) as being anticipated by Xia et al. (Bicrg. Med. Chem. Lett 6(7) 919-922, 1996).

Xia et al. teaches a series of substituted 1,3,5-triazines which includes compounds generically claimed herein for the use as cholesteryl ester transfer protein inhibitors. See formula 2 shown on page 919, the process for making these on page 920. See Table 1 for compounds made which includes those claimed herein.

Claims 1-12 and 43-53 lack novelty under PCT Article 33(2) as being anticipated by Coe et al. (US 5,536,722). Coe et al. teaches several trisubstituted triazines which include compounds claimed herein for the use as antitumor agents. See formula 1 and the definition of R₁-R₆ and various preferred embodiments on col. 2-5. See col. 5-7 for process of making these compounds and col. 7-16 for examples and details of the experimental procedure for making these compounds. Particularly note examples include compounds which have chiral centers as seen in example 16 and 17. But the reference is silent about the resolution. As stated above, Ueda et al. teaches the racemate of the instant optical isomers claimed herein. In absence of a purity limitation, the instantly claimed isomers read on the racemic mixture.

Claims 1-12 and 43-53 lack novelty under PCT Article 33(2) as being anticipated by Regnier et al. US 5,238,936.

Regnier et al. teaches several trisubstituted triazines which includes compounds claimed herein for the use as antitumor agents and as

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/10784

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

antiparasitic agents. See formula II and the definition of R₁-R₄, A and B and various preferred embodiments on col. 2-5. See col. 5-7 for process of making these compounds and col. 7-16 for examples, which details the experimental procedure for making these compounds. Particularly Table A for compounds which include those embraced herein.

Claims 13-42 and 54-55 meet the criteria set out in PCT Article 33(3), for inventive step as the triazine or thiazole compound and the method of use embraced in these claims are not obvious.

Claims 1-12 and 43-53 lack an inventive step under PCT Article 33(3) as being obvious over WO 99 05138 or EP 0 775 487 or Xia et al. or Coe et al. or Regnier et al.

Instant claims differ from the reference in reciting besides the racemate, the (+) and (-) form of the instant compounds. While reference does not discuss or silent about instant optical isomers, in view of the well-known existence of optical isomers where such is permissible and their resolution by techniques well-known in the art, it would have been obvious to one skilled in the art at the time the invention was made to expect the instant optical isomers of the racemate disclosed in reference to be also useful for the same use recited therein in view of the very close similarity.

Claims 1-55 meet the criteria set out in PCT Article 33(4), for industrial applicability as compounds embraced herein are useful as pharmaceuticals.

----- NEW CITATIONS -----

INTERNATIONAL PRELIMINARY EXAMINATION REPORTInternat~~ion~~ation No.

PCT/US00/10784

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. STATEMENT**

Novelty (N)	Claims <u>13-42 and 54-55</u>	YES
	Claims <u>1-12 and 43-53</u>	NO
Inventive Step (IS)	Claims <u>13-42 and 54-55</u>	YES
	Claims <u>1-12 and 43-53</u>	NO
Industrial Applicability (IA)	Claims <u>1-55</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS (Rule 70.7)

Please See Continuation Sheet

The demand must be filed directly with the competent International Preliminary Examining Authority or, if more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ US

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only

Identification of IPEA		Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 57743-A-PCT
International application No. PCT/US00/10784	International filing date (day/month/year) 21 April 2000	(Earliest) Priority date (day/month/year) 22 April 1999
Title of invention SELECTIVE NPY (Y5) ANTAGONISTS		
Box No. II APPLICANT(S)		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) SYNAPTIC PHARMACEUTICAL CORPORATION 215 College Road Paramus, New Jersey 07652-1410 United States of America		Telephone No.: None
		Facsimile No.: None
		Teleprinter No.: None
State (i.e. country) of nationality: United States of America		State (i.e. country) of residence: United States of America
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) MARZABADI, Mohammad R. 153 Woodland Avenue Ridgewood, New Jersey 07450 United States of America		
State (i.e. country) of nationality: United States of America		State (i.e. country) of residence: United States of America
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) WONG, Wai C. 314 Aspen Glen Drive Hamden, Connecticut 07450 United States of America		
State (i.e. country) of nationality: United States of America		State (i.e. country) of residence: United States of America
<input checked="" type="checkbox"/> Further applicants are indicated on a continuation sheet.		

Continuation of B x No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet is not to be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

NOBLE, Stewart A.
49 Stevenson Lane
Upper Saddle River, New Jersey 07458
United States of America

State (i.e. country) of nationality:

Great Britain

State (i.e. country) of residence:

United States of America

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

DESAI, Mahesh N.
29 Arthur Street
Clifton, New Jersey 07011
United States of America

State (i.e. country) of nationality:

United States of America

State (i.e. country) of residence:

United States of America

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

☐ Further applicants are indicated on another continuation sheet.

B x N . III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative
 and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

WHITE, John P.
 Cooper & Dunham LLP
 1185 Avenue of the Americas
 New York, New York 10036
 United States of America

Telephone No.:

(212) 278-0400

Facsimile No.:

(212) 391-0526

Teleprinter No.:

None

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

B x No. IV STATEMENT CONCERNING AMENDMENTS

The applicant wishes the International Preliminary Examining Authority*

- (i) ☐ to start the international preliminary examination on the basis of the international application as originally filed.
- (ii) ☐ to take into account the amendments under Article 34 of
- ☐ the description (amendments attached).
 - ☐ the claims (amendments attached).
 - ☐ the drawings (amendments attached).
- (iii) ☐ to take into account any amendments of the claims under Article 19 filed with the International Bureau (a copy is attached).
- (iv) ☐ to disregard any amendments of the claims made under Article 19 and to consider them as reversed.
- (v) ☐ to postpone the start of the international preliminary examination until the expiration of 20 months from the priority date unless that Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

B x No. V ELECTION OF STATES

☒ The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)* except.....

(If the applicant does not wish to elect certain eligible States, the name(s) or country code(s) of those States must be indicated above.)

Box N . VI CHECK LIST

The demand is accompanied by the following documents for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. amendments under Article 34 | | |
| description | : | sheets |
| claims | : | sheets |
| drawings | : | sheets |
| 2. letter accompanying amendments under Article 34 | : | sheets |
| 3. copy of amendments under Article 19 | : | sheets |
| 4. copy of statement under Article 19 | : | sheets |
| 5. other (specify): | : | sheets |

For International Preliminary
Examining Authority use only

received not received

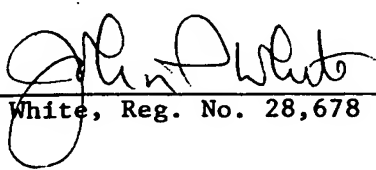
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. <input type="checkbox"/> separate signed power of attorney | 4. <input checked="" type="checkbox"/> fee calculation sheet |
| 2. <input type="checkbox"/> copy of general power of attorney | 5. <input checked="" type="checkbox"/> other (specify) Express Mail Certificate of Mailing bearing label no. EF299938198US, dated 22 November 2000 |
| 3. <input type="checkbox"/> statement explaining lack of signature | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).


John P. White, Reg. No. 28,678

22 November 2000
Date

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5. below. does not apply.

☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/10784

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C07D 251/70, 277/28, 513/04; A61K 31/427, 31/429, 31/53; A61P 3/04; 7/04, 9/12.
US CL : 544/198, 209; 548/151, 190, 193, 194; 514/245, 366.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/198, 209; 548/151, 190, 193, 194; 514/245, 366.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim N .
X	WO 99 05138 A1(ZENYAKU KOGYO KABUSHIKI KAISHA) 04 February 1999(04.02.1999), see entire document, especially page 12-14.	1-12 and 43-53
X	EP 0 775 487 A1(NIPPON SHINYAKU COMPAN7, LIMITED.) 28 May 1997(28.05.1997) , see entire document especially page s3-4 and pages 6-24.	1-12 and 43-53
X	US 5,536,722 A (COE et al.) 16 July 1996 (16.07.1996), see col. 2-5 and col. 7-16	1-12 and 43-53
X	US 5,238,936 A (REGNIER et al.) 24 August 1993 (24.08.1993), see col. 2-5 and col. 7-16.	1-12 and 43-53
X	XIA et al. Substituted 1,3,5-Triazines As Cholesteryl Ester Transfer Protein Inhibitors. Bioorg. Med. Chem. Lett. 1996, Vol. 6, No. 7, pages 919-922, especially see page 919-920	1-12 and 43-53
A	US 5,232,921 A (BIZIERE et al.) 03 August 1993 (03.08.1993), see entire document.	16-32 and 43-53



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T"

later documents published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

05 July 2000 (05.07.2000)

Date of mailing of the international search report

28 JUL 2000

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile N . (703)305-3230

Authorized officer

Venkataraman Balasubramanian

Telephone No. (703)308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/10784

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 1-32 and 33-55 (in part)
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application N .

PCT/US00/10784

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

- I. Claims 1-15 and 43-55 drawn to triazine compounds and pharmaceutical composition where the core ring is triazine
- II. Claims 16-32 and 43-55 drawn to compound of claim 16 and pharmaceutical composition where Y = S.
- III. Claims 16 and 43-55 drawn to compound of claim 16 and pharmaceutical composition where Y = O.
- IV. Claims 16 and 43-55 drawn to compound of claim 16 and pharmaceutical composition where Y = NH.
- V. Claims 33-55 drawn to compound of claim 33 and pharmaceutical composition where B = S.
- VI. Claims 33, 43-55 drawn to compound of claim 33 and pharmaceutical composition where B = O.
- VII. Claims 33, 43-55 drawn to compound of claim 33 and pharmaceutical composition where B = NH.

The inventions listed as Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Groups I-VII relate to structurally dissimilar compounds that lack common core namely triazine vs. thiazole vs. oxazole vs. imidazole vs. tricyclic thiazole vs tricyclic oxazole vs tricyclic imidazole which are not art recognized equivalent of each other. The sole feature common to the groups which does not vary is a ring with at least one nitrogen which by itself cannot be considered to define a novel contribution over prior art given such fragment with substituents is known in the prior art and therefore would not constitute a special technical feature as defined by PCT Rule 13.2.

PRESENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

WHITE, John, P.
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036
ETATS-UNIS D'AMERIQUE

RECEIVED
COOPER & DUNHAM

NOV 13 2000

DOCKET CLERK

IMPORTANT NOTICE

Date of mailing (day/month/year) 02 November 2000 (02.11.00)		
Applicant's or agent's file reference <u>57743-A-PCT</u>		
International application No. PCT/US00/10784	International filing date (day/month/year) 21 April 2000 (21.04.00)	Priority date (day/month/year) 22 April 1999 (22.04.99)
Applicant SYNAPTIC PHARMACEUTICAL CORPORATION et al		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

AU,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 02 November 2000 (02.11.00) under No. WO 00/64880

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No. (41-22) 740.14.35</p>	<p>Authorized officer J. Zahra</p> <p>Telephone No. (41-22) 338.83.38</p>
---	--

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

receiving office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference (if desired) (12 characters maximum) 57743-A-PCT

Box No. I TITLE OF INVENTION

SELECTIVE NPY (Y5) ANTAGONISTS

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

SYNAPTIC PHARMACEUTICAL CORPORATION
215 College Road
Paramus, New Jersey 07652-1410
United States of America

☐ This person is also inventor.

Telephone No.

None

Facsimile No.

None

Teleprinter No.

None

State (that is, country) of nationality:

United States of America

State (that is, country) of residence:

United States of America

This person is applicant for the purposes of:

☐ all designated States

☒ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

MARZABADI, Mohammad R.
153 Woodland Avenue
Ridgewood, New Jersey 07450
United States of America

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

United States of America

State (that is, country) of residence:

United States of America

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

☒ Further applicants and or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

WHITE, John P.
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
United States of America

Telephone No.

(212) 278-0400

Facsimile No.

(212) 391-0526

Teleprinter No.

None

☐ Address for correspondence: Mark this check-box where no agent or common representative is has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

WONG, Wai C.
314 Aspen Glen Drive
Hamden, Connecticut 07450
United States of America

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

United States of America

State (that is, country) of residence:

United States of America

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

NOBLE, Stewart A.
49 Stevenson Lane
Upper Saddle River, New Jersey 07458
United States of America

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

Great Britain

State (that is, country) of residence:

United States of America

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

DESAI, Mahesh N.
29 Arthur Street
Clifton, New Jersey 07011
United States of America

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

United States of America

State (that is, country) of residence:

United States of America

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|---|---|
| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> LR Liberia |
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LS Lesotho |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> MA Morocco |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CR Costa Rica | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> DM Dominica | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GD Grenada | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> TZ United Republic of Tanzania |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> IN India | |
| <input checked="" type="checkbox"/> IS Iceland | |
| <input checked="" type="checkbox"/> JP Japan | |
| <input checked="" type="checkbox"/> KE Kenya | |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | |
| <input checked="" type="checkbox"/> KR Republic of Korea | |
| <input checked="" type="checkbox"/> KZ Kazakhstan | |
| <input checked="" type="checkbox"/> LC Saint Lucia | |
| <input checked="" type="checkbox"/> LK Sri Lanka | |
| | <input checked="" type="checkbox"/> UZ Uzbekistan |
| | <input checked="" type="checkbox"/> VN Viet Nam |
| | <input checked="" type="checkbox"/> YU Yugoslavia |
| | <input checked="" type="checkbox"/> ZA South Africa |
| | <input checked="" type="checkbox"/> ZW Zimbabwe |

continuation-in-part. (see Page 5)

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ **MZ** Mozambique

☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claims indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 22.04.99 (22 April 1999)	09/296,332	US		
item (2) 30.06.99 (30 June 1999)	09/343,994	US		
item (3) 30.06.99 (30 June 1999)	09/343,762	US		

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): 1-3

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(iii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / US

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)

Number

Country (or regional Office)

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request : 6
description (excluding sequence listing part) : 238
claims : 42
abstract : 1
drawings : 6
sequence listing part of description : 0

Total number of sheets : 293

This international application is accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other (specify): Transmittal Letter

Figure of the drawings which should accompany the abstract:

Language of filing of the international application:

English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

SYNAPTIC PHARMACEUTICAL CORPORATION

NAME: Kathleen P. Mullinix
TITLE: President

April 19, 2000
Date

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	
6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.	

Date of receipt of the record copy by the International Bureau:

For International Bureau use only

Box No. VI PRIORITY CLAIM

☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 22.04.99 (22 April 1999)	09/296,332	US		
item (2) 30.06.99 (30 June 1999)	09/343,994	US		
item (3) 30.06.99 (30 June 1999)	09/343,762	US		

- ☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): 1-3
- * Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / US

Request to use results of earlier search: reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)

Number

Country (or regional Office)

Box No. VIII CHECK LIST: LANGUAGE OF FILING

This international application contains the following number of sheets:

request : 6

description (excluding sequence listing part) : 238

claims : 42

abstract : 1

drawings : 6

sequence listing part of description : 0

Total number of sheets : 293

This international application is accompanied by the item(s) marked below:

1. ☒ fee calculation sheet2. ☐ separate signed power of attorney3. ☐ copy of general power of attorney: reference number, if any:4. ☐ statement explaining lack of signature5. ☐ priority document(s) identified in Box No. VI as item(s):6. ☐ translation of international application into (language):7. ☐ separate indications concerning deposited microorganism or other biological material8. ☐ nucleotide and/or amino acid sequence listing in computer readable form9. ☒ other (specify): Transmittal Letter

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Mohammad R. Marzabadi 4/19/2000
Mohammad R. Marzabadi Date

Stewart A. Noble

Date

Wai C. Wong

Date

Mahesh N. Desai
Mahesh N. Desai

4/19/2000
Date

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	
6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.	

For International Bureau use only

Date of receipt of the received copy by the International Bureau:

Supplemental Box

If the Supplemental Box is not used, this sheet should not be included in the request.

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

- (i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
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Continuation of Box V.: U.S. Serial No. 09/296,332, filed April 22, 1999, U.S.
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Serial No. 09/343,762, filed June 30, 1999.

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(22) International Filing Date: 21 April 2000 (21.04.00)		(75) Inventors/Applicants (for US only): MARZABADI, Moham- mad, R. [US/US]; 153 Woodland Avenue, Ridgewood, NJ 07450 (US). WONG, Wai, C. [US/US]; 314 Aspen Glen Drive, Hamden, CT 07450 (US). NOBLE, Stewart, A. [GB/US]; 49 Stevenson Lane, Upper Saddle River, NJ 07458 (US). DESAI, Mahesh, N. [US/US]; 29 Arthur Street, Clifton, NJ 07011 (US).	
(30) Priority Data: 09/296,332 22 April 1999 (22.04.99) US 09/343,994 30 June 1999 (30.06.99) US 09/343,762 30 June 1999 (30.06.99) US		(74) Agent: WHITE, John, P.; Cooper & Dunham LLP, 1185 Avenue of the Americas, New York, NY 10036 (US).	
(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications US 09/343,994 (CIP) Filed on 30 June 1999 (30.06.99) US 09/343,762 (CIP) Filed on 30 June 1999 (30.06.99) US 09/296,332 (CIP) Filed on 22 April 1999 (22.04.99)		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except US): SYNAPTIC PHARMACEUTICAL CORPORATION [US/US]; 215 Col- lege Road, Paramus, NJ 07652-1410 (US).		Published <i>With international search report.</i>	
(54) Title: SELECTIVE NPY (Y5) ANTAGONISTS			
(57) Abstract <p>This invention is directed to triazine derivatives, bicyclic compounds and tricyclic compounds which are selective antagonists for a NPY (Y5) receptor. The invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier. This invention provides a pharmaceutical composition made by combining a therapeutically effective amount of a compound of this invention and a pharmaceutically acceptable carrier. This invention provides a process for making a pharmaceutical composition comprising combining a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier. The invention further provides the use of a compound of the invention for the preparation of a pharmaceutical composition for treating an abnormality, wherein the abnormality is alleviated by decreasing the activity of a human Y5 receptor.</p>			

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SELECTIVE NPY (Y5) ANTAGONISTS5 Background Of The Invention

This application claims priority of and is a continuation-in-part of U.S. Serial No. 09/296,332, filed April 22, 1999, U.S. Serial No. 09/343,762, filed June 30, 1999, and
10 U.S. Serial No. 09/343,994, filed June 30, 1999, the contents of all of which are hereby incorporated by reference into the subject application.

Throughout this application, various references are
15 referred to within parentheses. Disclosures of these publications in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains. Full bibliographic citations for these references may be
20 found at the end of this application, preceding the claims.

The peptide neurotransmitter neuropeptide Y (NPY) is a 36 amino acid member of the pancreatic polypeptide family
25 with widespread distribution throughout the mammalian nervous system (Dumont et al., 1992). The family includes the pancreatic polypeptide (PP), synthesized primarily by endocrine cells in the pancreas; peptide YY (PYY), synthesized primarily by endocrine cells in the gut; and
30 NPY, synthesized primarily in neurons (Michel, 1991; Dumont et al., 1992; Wahlestedt and Reis, 1993). All pancreatic polypeptide family members share a compact structure involving a "PP-fold" and a conserved C-terminal hexapeptide ending in Tyr³⁶ (or Y³⁶ in the single letter
35 code). The striking conservation of Y³⁶ has prompted the

reference to the pancreatic polypeptides' receptors as "Y-type" receptors (Wahlestedt et al., 1987), all of which are proposed to function as seven transmembrane-spanning G protein-coupled receptors (Dumont et al., 1992).

5

NPY and its relatives elicit a broad range of physiological effects through activation of at least five G protein-coupled receptor subtypes known as Y1, Y2, Y3, Y4 (or PP), and the "atypical Y1". While the Y1, Y2, Y3, and Y4 (or PP) receptors were each described previously in both radioligand binding and functional assays, the "atypical Y1" receptor is unique in that its classification is based solely on feeding behavior induced by various peptides including NPY.

15

The role of NPY in normal and abnormal eating behavior, and the ability to interfere with NPY-dependent pathways as a means to appetite and weight control, are areas of great interest in pharmacological and pharmaceutical research (Sahu and Kalra, 1993; Dryden et al., 1994). NPY is considered to be the most powerful stimulant of feeding behavior yet described (Clark et al., 1984; Levine and Morley, 1984; Stanley and Leibowitz, 1984). The stimulation of feeding behavior by NPY is thought to occur primarily through activation of the hypothalamic "atypical Y1" receptor. For example, direct injection of NPY into the hypothalamus of satiated rats can increase food intake up to 10-fold over a 4-hour period (Stanley et al., 1992). Similar studies using other peptides has resulted in a pharmacologic profile for the "atypical Y1" receptor according to the rank order of potencies of peptides in stimulating feeding behavior as follows: NPY₂₋₃₆ ~ NPY ~ PYY ~ [Leu³¹,Pro³⁴]NPY > NPY₁₃₋₃₆ (Kalra et al., 1991; Stanley et al., 1992). The profile is similar to that of

30

a Y1-like receptor except for the anomalous ability of NPY₂₋₃₆ to stimulate food intake with potency equivalent or better than that of NPY. A subsequent report in J. Med. Chem. by Balasubramaniam and co-workers (1994) showed that feeding can be regulated by [D-Trp³²]NPY. While this peptide was presented as an NPY antagonist, the published data at least in part support a stimulatory effect of [D-Trp³²]NPY on feeding. In contrast to other NPY receptor subtypes, the "feeding" receptor has never been characterized for peptide binding affinity in radioligand binding assays.

This problem has been addressed by cloning rat and human cDNAs which encode a single receptor protein, referred to herein as Y5, whose pharmacologic profile links it to the "atypical Y1" receptor. The identification and characterization of a single molecular entity which explains the "atypical Y1" receptor allows the design of selective drugs which modulate feeding behavior (WO 96/16542). It is important to note, though, that any credible means of studying or modifying NPY-dependent feeding behavior must necessarily be highly selective, as NPY interacts with multiple receptor subtypes, as noted above (Dumont et al., 1992).

As used in this invention, the term "antagonist" refers to a compound which binds to, and decreases the activity of, a receptor in the presence of an agonist. In the case of a G-protein coupled receptor, activation may be measured using any appropriate second messenger system which is coupled to the receptor in a cell or tissue in which the receptor is expressed. Some specific but by no means limiting examples of well-known second messenger systems are adenylate cyclase, intracellular calcium mobilization,

ion channel activation, guanylate cyclase, and inositol phospholipid hydrolysis. Conversely, the term "agonist" refers to a compound which binds to, and increases the activity of, a receptor as compared with the activity of the receptor in the absence of any agonist.

In order to test compounds for selective binding to the human Y5 receptor the cloned cDNAs encoding both the human and rat Y2 and Y4 (or PP) receptors have been used. The human and rat Y5 receptors are described in coassigned U.S. Patent No. 5,602,024 and in PCT International Application US95/15646, published June 6, 1996, as WO 96/16542, the contents of which are hereby incorporated by reference into this application. The human and rat Y2 receptors are described in coassigned U.S. Patent No. 5,545,549 and in PCT International Application US95/01469, published August 10, 1995, as WO 95/21245, the contents of which are hereby incorporated by reference into this application. The human and rat Y4 receptors are described in coassigned U.S. Patent No. 5,516,653 and in PCT International Application PCT/US94/14436, published July 6, 1995, as WO 95/17906, the contents of which are hereby incorporated by reference into this application. The Y1 receptor has been cloned from a variety of species including human, rat and mouse (Larhammar et al., 1992; Herzog et al., 1992; Eva et al., 1990; Eva et al., 1992).

Using the NPY-Y5-selective antagonist CGP 71683A, it was demonstrated recently that food intake in free-feeding and energy-derived lean rats is mediated by the Y5 receptor (Criscione et al., 1998). CGP 71683A has high affinity for the cloned rat NPY-Y5 receptor subtype, but 1,000-fold lower affinity for the cloned rat NPY-Y1, Y2, and Y4 receptors. Examples of additional NPY-Y5-selective

compounds are disclosed in WO 97/20823, WO 98/35957, and WO 98/35944.

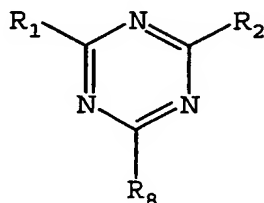
5 In different embodiments of this invention the synthesis of novel triazine compounds, bicyclic compounds and tricyclic compounds which bind selectively to the cloned human Y5 receptor, compared to the other cloned human NPY receptors, and inhibit the activation of the cloned human Y5 receptor as measured in in vitro assays is disclosed.

10 The in vitro receptor binding and activation assays described hereinafter were performed using various cultured cell lines, each transfected with and expressing only a single Y-type receptor.

15 In addition, the compounds of the present invention may be used to treat abnormal conditions such as feeding disorders (obesity and bulimia nervosa), sexual/reproductive disorders, depression, epileptic seizure, hypertension, cerebral hemorrhage, congestive
20 heart failure, sleep disturbances, or any condition in which antagonism of a Y5 receptor may be beneficial.

Summary Of The Invention

This invention provides a compound having the structure



5

wherein R_1 is F; Cl; Br; I; NR_3R_4 ; or phenyl or heteroaryl;
 wherein the phenyl or heteroaryl may be substituted with
 one or more of F, Cl, Br, I, -CN, -NO₂, -NR₅R₆, -
 SO₂R₅, - (CH₂)_nC(Y)R₇, - (CH₂)_nYR₅, - (CH₂)_nC(Y)NR₅R₆, -
 (CH₂)_nNR₅C(Y)R₅, - (CH₂)_nCO₂R₅, - (CH₂)_nSO₂NR₅R₆, a straight
 chained or branched C₁-C₇ alkyl, monofluoroalkyl,
 polyfluoroalkyl, aminoalkyl, C₂-C₇ alkenyl or C₂-C₇
 alkynyl, or a C₃-C₇ cycloalkyl or cycloalkenyl;

15

wherein R_2 is NR_3R_4 ;

wherein R_3 is independently H; - (CH₂)_uYR₅; -
 (CH₂)_tC(Y)NR₅R₆; - (CH₂)_uNR₅C(Y)R₅; - (CH₂)_tC(Y)R₇; -
 (CH₂)_tCO₂R₅; - (CH₂)_uNR₅R₆; - (CH₂)_uCN; - C(Y)R₅; -
 C(Y)NR₅R₆; - CO₂R₅; straight chained or branched C₁-C₇
 alkyl, C₂-C₇ alkenyl, or C₂-C₇ alkynyl; C₃-C₇ cycloalkyl or
 cycloalkenyl; phenyl; C₁-C₆ phenylalkyl; or C₁-C₆
 heteroarylalkyl; wherein the phenyl, C₁-C₆ phenylalkyl, or
 C₁-C₆ heteroarylalkyl may be substituted with one or more
 of F, Cl, Br, I, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -
 (CH₂)_nC(Y)R₇, - (CH₂)_nYR₅, - (CH₂)_nC(Y)NR₅R₆, -
 (CH₂)_nNR₅C(Y)R₅, - (CH₂)_nCO₂R₅, - (CH₂)_nSO₂NR₅R₆, a straight
 chained or branched C₁-C₇ alkyl, monofluoroalkyl,

25

polyfluoroalkyl, aminoalkyl, C₂-C₇ alkenyl or C₂-C₇ alkynyl, or a C₃-C₇ cycloalkyl or cycloalkenyl;

wherein R₄ is independently H; -(CH₂)_uYR₅; -
 5 (CH₂)_tC(Y)NR₅R₆; -(CH₂)_uNR₅C(Y)R₅; -(CH₂)_tC(Y)R₇; -
 (CH₂)_tCO₂R₅; -(CH₂)_uNR₅R₆; -(CH₂)_uCN; straight chained or
 branched C₁-C₇ alkyl; straight chained or branched C₂-C₇
 alkenyl or C₂-C₇ alkynyl; C₃-C₇ cycloalkyl or cycloalkenyl;
 phenyl; or C₁-C₆ phenylalkyl; wherein the phenyl or C₁-C₆
 10 phenylalkyl may be substituted with one or more of F, Cl,
 Br, I, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nC(Y)R₇, -
 (CH₂)_nYR₅, -(CH₂)_nC(Y)NR₅R₆, -(CH₂)_nNR₅C(Y)R₅, -(CH₂)_nCO₂R₅,
 -(CH₂)_nSO₂NR₅R₆, a straight chained or branched C₁-C₇ alkyl,
 monofluoroalkyl, polyfluoroalkyl, aminoalkyl, C₂-C₇
 15 alkenyl or C₂-C₇ alkynyl, or a C₃-C₇ cycloalkyl or
 cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to
 which they are attached are 1-azetidiny, 1-
 20 pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl, wherein
 the 1-azetidiny, 1-pyrrolidinyl, 1-piperidinyl, or
 1H-azepanyl is substituted with one or more of F,
 -CN, -(CH₂)_nNR₅R₆, -SO₂R₅, -(CH₂)_nC(Y)R₇, -(CH₂)_nYR₅,
 -(CH₂)_nC(Y)NR₅R₆, -(CH₂)_nNR₅C(Y)R₅, -(CH₂)_nCO₂R₅, a straight
 25 chained or branched C₁-C₇ alkyl, monofluoroalkyl,
 polyfluoroalkyl, aminoalkyl, a C₂-C₇ alkenyl or C₂-C₇
 alkynyl, a C₃-C₇ cycloalkyl or cycloalkenyl, or phenyl or
 heteroaryl; wherein if -(CH₂)_nNR₅R₆, -(CH₂)_nYR₅, or -
 (CH₂)_nNR₅C(Y)R₅ are in the 2-position, then n is not 0;
 30 wherein the phenyl or heteroaryl may be substituted with
 one or more of F, Cl, Br, I, -CN, -NO₂, -NR₅R₆, -
 SO₂R₅, -(CH₂)_nC(Y)R₇, -(CH₂)_nYR₅, -(CH₂)_nC(Y)NR₅R₆, -
 (CH₂)_nNR₅C(Y)R₅, -(CH₂)_nCO₂R₅, -(CH₂)_nSO₂NR₅R₆, a straight
 chained or branched C₁-C₇ alkyl, monofluoroalkyl,

polyfluoroalkyl, aminoalkyl, a C₂-C₇ alkenyl or C₂-C₇ alkynyl, or a C₃-C₇ cycloalkyl or cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to which they are attached are morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl, wherein the morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl is substituted with one or more straight chained or branched C₁-C₇ alkyl or C₁-C₇ phenylalkyl; and wherein the nitrogen atom of the piperazinyl or [1,4]diazepanyl ring is substituted with - (CH₂)_uYR₅; - (CH₂)_tC(Y)NR₅R₆; - (CH₂)_uNR₅C(Y)R₅; - (CH₂)_tC(Y)R₇; - (CH₂)_tCO₂R₅; - (CH₂)_uNR₅R₆; - (CH₂)_uCN; - C(Y)R₅; - C(Y)NR₅R₆; - CO₂R₅; straight chained or branched C₁-C₇ alkyl, C₂-C₇ alkenyl, or C₂-C₇ alkynyl; or C₃-C₇ cycloalkyl or cycloalkenyl; phenyl; C₁-C₆ phenylalkyl; or C₁-C₆ heteroarylalkyl; wherein the phenyl, C₁-C₆ phenylalkyl, or C₁-C₆ heteroarylalkyl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -NR₅R₆, -SO₂R₅, - (CH₂)_nC(Y)R₇, - (CH₂)_nYR₅, - (CH₂)_nC(Y)NR₅R₆, - (CH₂)_nNR₅C(Y)R₅, - (CH₂)_nCO₂R₅, - (CH₂)_nSO₂NR₅R₆, a straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, a C₂-C₇ alkenyl or C₂-C₇ alkynyl, or a C₃-C₇ cycloalkyl or cycloalkenyl;

wherein each of R₅, R₆ and R₇ is independently H; or straight chained or branched C₁-C₇ alkyl;

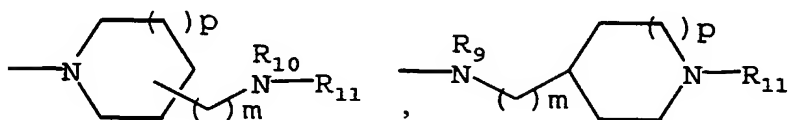
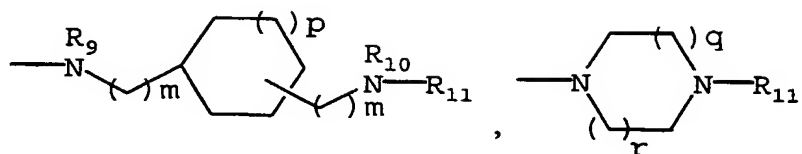
wherein each n is independently an integer from 0 to 6 inclusive;

wherein each t is independently an integer from 1 to 4 inclusive;

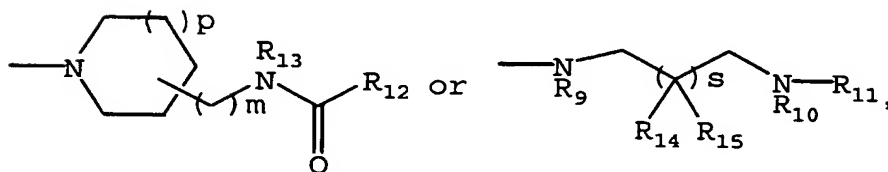
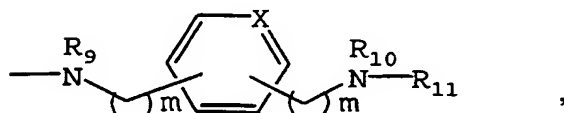
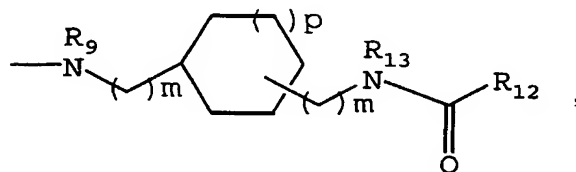
wherein each u is independently an integer from 2 to 4 inclusive;

5 wherein Y is O or S;

wherein R₈ is



10



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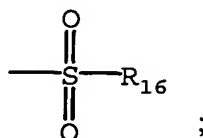
provided that if R₈ contains a piperidinyl group and m is 0, then the compound is not an -aminal-containing compound;

20

wherein each of R_9 and R_{10} is independently H; straight chained or branched C_1 - C_4 alkyl;

5

wherein R_{11} is H or



10

wherein R_{12} is H;

wherein R_{13} is independently H; $-(\text{CH}_2)_u\text{YR}_5$; $-(\text{CH}_2)_t\text{C}(\text{Y})\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{NR}_5\text{C}(\text{Y})\text{R}_5$; $-(\text{CH}_2)_t\text{C}(\text{Y})\text{R}_7$; $-(\text{CH}_2)_t\text{CO}_2\text{R}_5$; $-(\text{CH}_2)_u\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{CN}$; $-\text{C}(\text{Y})\text{R}_5$; $-\text{C}(\text{Y})\text{NR}_5\text{R}_6$; $-\text{CO}_2\text{R}_5$; straight chained or branched C_1 - C_7 alkyl; C_1 - C_7 alkyl substituted with one or more F or Cl; C_3 - C_7 cycloalkyl- C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl, or alkynyl; or C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl or C_1 - C_6 phenylalkyl; wherein the phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F, Cl, $-\text{CN}$, $-\text{NO}_2$, $-\text{NR}_5\text{R}_6$, $-\text{SO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{C}(\text{Y})\text{R}_7$, $-(\text{CH}_2)_n\text{YR}_5$, $-(\text{CH}_2)_n\text{C}(\text{Y})\text{NR}_5\text{R}_6$, $-(\text{CH}_2)_n\text{NR}_5\text{C}(\text{Y})\text{R}_5$, $-(\text{CH}_2)_n\text{CO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{SO}_2\text{NR}_5\text{R}_6$, a straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, a C_2 - C_7 alkenyl or C_2 - C_7 alkynyl, or a C_3 - C_7 cycloalkyl or cycloalkenyl;

30

or R_{12} and R_{13} together with the amide linkage to which they are attached are pyrrolidinonyl or piperidonyl;

wherein R_{14} is H; straight chained or branched C_1 - C_7 alkyl; F; or $-(\text{CH}_2)_n\text{OR}_5$;

wherein R_{15} is H, straight chained or branched C_1 - C_7 alkyl, or F;

5 wherein R_{16} is NR_3R_4 , unsubstituted straight chained or branched C_2 - C_7 alkyl, substituted straight chained or branched C_1 - C_7 alkyl, wherein the C_1 - C_7 alkyl may be substituted with one or more of F, Cl, -CN, - NR_5R_6 , -
10 SO_2R_5 , - $(CH_2)_n C(Y)R_7$, - $(CH_2)_n YR_5$, - $(CH_2)_n C(Y)NR_5R_6$, -
 $(CH_2)_n NR_5C(Y)R_5$, - $(CH_2)_n CO_2R_5$, - $(CH_2)_n OCF_3$, monofluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or C_2 - C_7 alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl, phenyl, heteroaryl, or C_1 - C_7 phenylalkyl, wherein the phenyl, heteroaryl, or C_1 - C_7
15 phenylalkyl may be substituted with one or more of F, Cl, Br, I, -CN, - NO_2 , - NR_5R_6 , - $(CH_2)_n NR_5C(Y)R_5$, -
 SO_2R_5 , - $(CH_2)_n C(Y)R_7$, - $(CH_2)_n YR_5$, - $(CH_2)_n C(Y)NR_5R_6$, -
 $(CH_2)_n CO_2R_5$, - $(CH_2)_n SO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight chained or branched C_1 - C_7 alkyl,
20 monofluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl; quinolinyl, 1-naphthyl, 2-naphthyl, or 2,1,3-benzothiadiazolyl; with the provisos that when R_1 is F, Cl, Br, or I, then R_{16} is 1-naphthyl; and when R_1 and R_2 are morpholinyl, then R_{16} is
25 not NR_3R_4 ;

wherein each m is independently an integer from 0 to 3 inclusive;

30

wherein each s is independently an integer from 1 to 6 inclusive;

12

wherein each p is independently an integer from 0 to 2 inclusive;

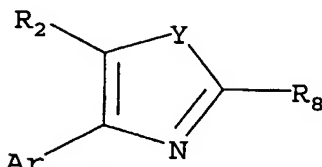
5 wherein each q is independently an integer from 1 to 2 inclusive;

wherein each r is independently an integer from 1 to 2 inclusive;

10 wherein X is N or C;

or a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:



wherein Y is O, S or NH;

5

wherein Ar is a heteroaryl ring that may be optionally substituted with one or more R_1 groups;

10

wherein each R_1 independently is H, F, Cl, Br, -CN, -OH, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, -SO₂C₆H₅, -SO₂NR₅R₆, -C₆H₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, ethylenedioxy, methylenedioxy, perfluoroalkyl, polyfluoroalkyl, aminoalkyl, or straight chained or branched C₁-C₇ alkyl; or phenyl, heteroaryl, or C₁-C₇ phenylalkyl, wherein the phenyl, heteroaryl, or C₁-C₇ phenylalkyl may be substituted with one or more of F, Cl, Br, -CF₃, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, or straight chained or branched C₁-C₄ alkyl;

15

20

wherein R_2 is H, straight chained or branched C₁-C₄ alkyl, -(CH₂)_tOR₅, phenyl optionally substituted with one or more of F, Cl, Br, -CF₃, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, or straight chained or branched C₁-C₄ alkyl;

25

wherein R_5 is independently H; or straight chained or branched C₁-C₇ alkyl;

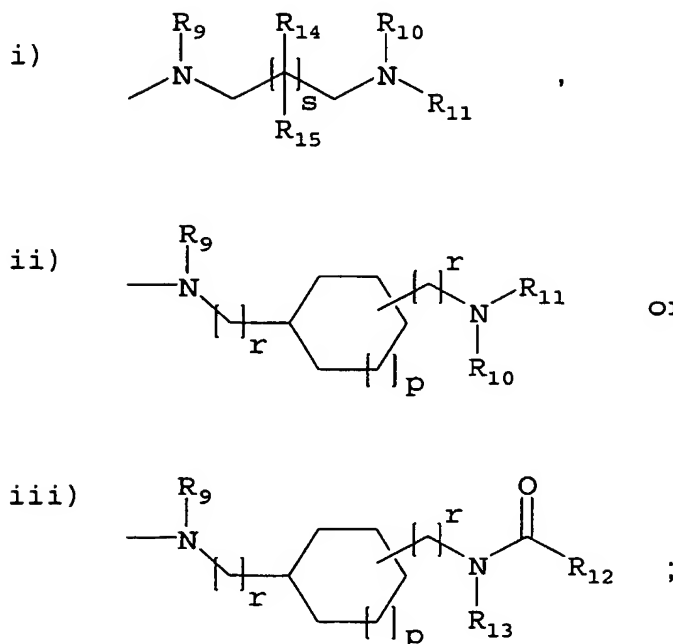
wherein R_6 is independently H; or straight chained or branched C₁-C₇ alkyl;

30

wherein each n independently is an integer from 0 to 6 inclusive;

wherein R₈ is

5



provided that when R₈ is (iii), and Ar is thiazol-2-yl, R₁ cannot be H;

10

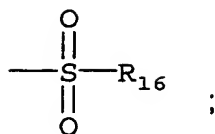
wherein R₉ is independently H; or straight chained or branched C₁-C₄ alkyl;

wherein R₁₀ is independently H; or straight chained or branched C₁-C₄ alkyl;

15

20

wherein R_{11} is



5 wherein R_{12} is H, straight chained or branched C_1 - C_7 alkyl; or $(\text{CH}_2)_n\text{OR}_{17}$;

wherein R_{13} is independently $-(\text{CH}_2)_u\text{OR}_5$; $-(\text{CH}_2)_t\text{CONR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{NR}_5\text{COR}_5$; $-(\text{CH}_2)_t\text{COR}_7$; $-(\text{CH}_2)_t\text{CO}_2\text{R}_5$; $-(\text{CH}_2)_u\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{CN}$; straight chained or
 10 branched C_1 - C_7 alkyl; C_1 - C_7 alkyl in which the C_2 - C_7 atoms may be optionally substituted with one or more F or Cl; C_3 - C_7 cycloalkyl- C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl; or C_3 - C_5 cycloalkyl;

15

or R_{12} and R_{13} together with the amide linkage to which they are attached are pyrrolidinonyl, piperidonyl, or oxazolidinonyl;

20 wherein R_7 is independently straight chained or branched C_1 - C_7 alkyl;

wherein R_{14} is H; straight chained or branched C_1 - C_4 alkyl; F; or $-(\text{CH}_2)_r\text{OR}_5$;

25

wherein R_{15} is H, straight chained or branched C_1 - C_4 alkyl, or F;

with the proviso that when R_{14} is -OH, R_{15} cannot be F;

30

wherein R_{16} is $-NR_3R_4$, perfluoroalkyl, unsubstituted straight chained or branched C_2-C_7 alkyl, substituted straight chained or branched C_2-C_7 alkyl, wherein the C_2-C_7 alkyl may be substituted with one or more of F, Cl, -CN, $-NR_5R_6$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nOCF_3$, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, or C_3-C_7 cycloalkyl; C_3-C_7 cycloalkyl; phenyl, thienyl, isoxazolyl, quinoliny, or C_1-C_7 phenylalkyl, wherein the phenyl, thienyl, isoxazolyl, quinoliny, or C_1-C_7 phenylalkyl may be substituted with one or more of F, Cl, Br, I, -CN, $-NO_2$, $-NR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight chained or branched C_1-C_3 alkyl, perfluoroalkyl, or aminoalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, or C_3-C_7 cycloalkyl or cycloalkenyl; quinoliny, 1-naphthyl, 2-naphthyl, or 2,1,3-benzothiadiazolyl; wherein the quinoliny, 1-naphthyl, 2-naphthyl or 2,1,3-benzothiadiazolyl may be substituted with one or more of F, Cl, Br, -CN, $-NO_2$, $-NR_5R_6$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, straight chained or branched C_1-C_4 alkyl, perfluoroalkyl, or aminoalkyl;

25

provided that when R_{16} is quinoliny and R_8 is (ii), Ar cannot be pyrrolyl;

30

provided that when R_{16} is $N(CH_3)_2$ and R_8 is (i), Ar cannot be thiazol-2-yl;

wherein R_3 is independently H; $-(CH_2)_uOR_5$; $-(CH_2)_tCONR_5R_6$; $-(CH_2)_uNR_5COR_5$; $-(CH_2)_tCOR_7$; $-(CH_2)_tCO_2R_5$; $-(CH_2)_uNR_5R_6$; $-(CH_2)_uCN$; straight chained or

5 branched C₁-C₇ alkyl; straight chained or branched C₂-C₇
 alkenyl or alkynyl; or C₃-C₇ cycloalkyl or cycloalkenyl;
 phenyl, or C₁-C₆ phenylalkyl; wherein the phenyl, or C₁-C₆
 phenylalkyl may be substituted with one or more of F, Cl,
 10 Br, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nCOR₇, -
 (CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, -(CH₂)_nCO₂R₅, -
 (CH₂)_nSO₂NR₅R₆, straight chained or branched C₁-C₇ alkyl,
 perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight
 15 chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇
 cycloalkyl or cycloalkenyl;

wherein R₄ is independently H; -(CH₂)_uOR₅; -
 (CH₂)_tCONR₅R₆; -(CH₂)_uNR₅COR₅; -(CH₂)_tCOR₇; -
 (CH₂)_tCO₂R₅; -(CH₂)_uNR₅R₆; -(CH₂)_uCN; straight chained or
 15 branched C₁-C₇ alkyl; straight chained or branched C₂-C₇
 alkenyl or alkynyl; or C₃-C₇ cycloalkyl or cycloalkenyl;
 phenyl or C₁-C₆ phenylalkyl; wherein the phenyl or C₁-C₆
 phenylalkyl may be substituted with one or more of F, Cl,
 20 Br, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nCOR₇, -
 (CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, -
 (CH₂)_nCO₂R₅, -(CH₂)_nSO₂NR₅R₆, straight chained or branched C₁-
 C₇ alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl,
 25 straight chained or branched C₂-C₇ alkenyl or alkynyl, or
 C₃-C₇ cycloalkyl or cycloalkenyl;

25 or R₃ and R₄ taken together with the nitrogen atom to which
 they are attached are 1-azetidiny, 1-pyrrolidinyl, 1-
 piperidinyl, or 1H-azepanyl, wherein the 1-azetidiny, 1-
 pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl is substituted
 30 with one or more of F, -CN, -(CH₂)_nNR₅R₆, -SO₂R₅, -
 (CH₂)_nCOR₇, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, -
 (CH₂)_nCO₂R₅, straight chained or branched C₁-C₇ alkyl,
 perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight
 35 chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇

cycloalkyl or cycloalkenyl, or phenyl or thienyl, or isoxazolyl, or quinolinyl; wherein if $-(CH_2)_nNR_5R_6$, $-(CH_2)_nOR_5$, or $-(CH_2)_nNR_5COR_5$ are in the 2-position, then n is not 0; wherein the phenyl, thienyl, isoxazolyl, or quinolinyl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -NR₅R₆, -SO₂R₅, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, straight chained or branched C₁-C₇ alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to which they are attached are morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl, wherein the morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl is optionally substituted with straight chained or branched C₁-C₅ alkyl or $-(CH_2)_tOR_5$; and wherein the nitrogen atom of the piperazinyl or [1,4]diazepanyl ring may be optionally substituted with $-(CH_2)_uOR_5$; -COR₅; straight chained or branched C₁-C₅ alkyl; or phenyl; wherein the phenyl may be substituted with one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, $-(CH_2)_nOR_5$, straight chained or branched C₁-C₃ alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

wherein R₁₇ is straight chained or branched C₁-C₄ alkyl, perfluoroalkyl, or polyfluoroalkyl;

wherein each p independently is an integer from 0 to 2 inclusive;

wherein each r independently is an integer from 0 to 3 inclusive;

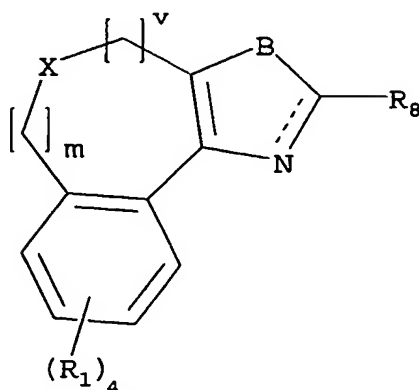
5 wherein each s independently is an integer from 3 to 6 inclusive;

wherein t is an integer from 1 to 4 inclusive;

10 wherein each u independently is an integer from 2 to 4 inclusive;

or a pharmaceutically acceptable salt thereof.

The invention provides a compound having the structure:



wherein each R_1 is independently H, F, Cl, Br, -CN, -OH, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, - (CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, perfluoroalkyl, polyfluoroalkyl, aminoalkyl, or straight chained or branched C₁-C₇ alkyl;

wherein R_5 is independently H; or straight chained or branched C₁-C₇ alkyl;

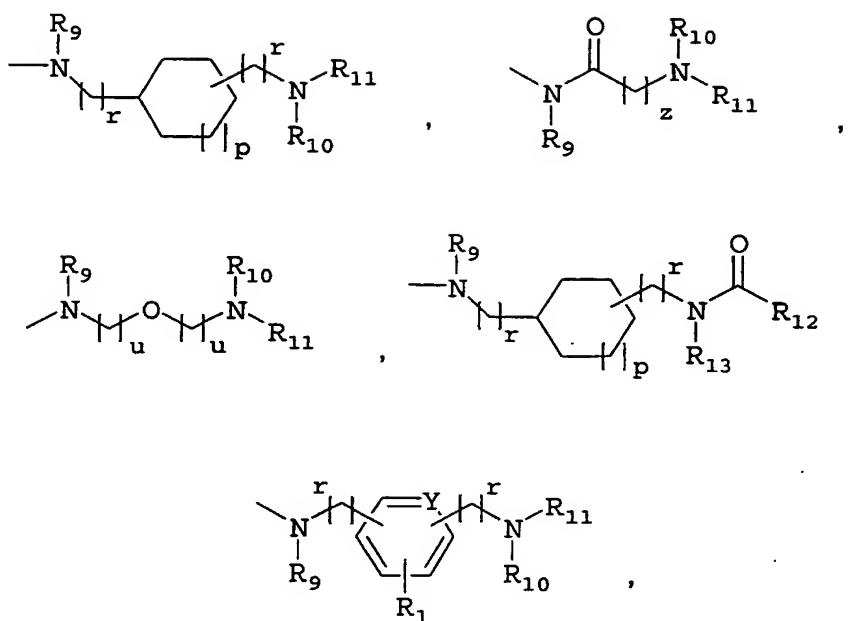
wherein R_6 is independently H; or straight chained or branched C₁-C₇ alkyl;

wherein B is O, NH or S;

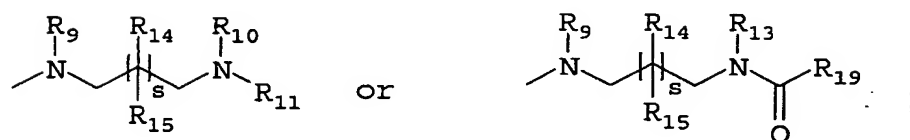
wherein X is S, SO or SO₂;

wherein each n independently is an integer from 0 to 6 inclusive;

wherein R_8 is



5



wherein Y is C or N;

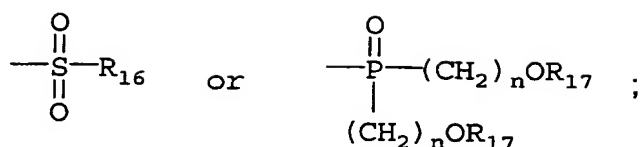
10 wherein R_7 is independently straight chained or branched C_1 - C_7 alkyl;

wherein R_9 is independently H; or straight chained or branched C_1 - C_4 alkyl;

15

wherein R_{10} is independently H; or straight chained or branched C_1 - C_4 alkyl;

wherein R_{11} is



5 wherein R_{12} is H, straight chained or branched C_1 - C_7 alkyl, $(\text{CH}_2)_u\text{OR}_{17}$, or $\text{O}(\text{CH}_2)_u\text{OR}_{17}$; provided that when X is O, R_{12} cannot be methyl;

10 wherein R_{13} is independently H; $-(\text{CH}_2)_u\text{OR}_5$; $-(\text{CH}_2)_t\text{CONR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{NR}_5\text{COR}_5$; $-(\text{CH}_2)_t\text{COR}_7$; $-(\text{CH}_2)_t\text{CO}_2\text{R}_5$; $-(\text{CH}_2)_u\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{CN}$; straight chained or branched C_1 - C_7 alkyl; C_1 - C_7 alkyl in which the C_2 - C_7 atoms may be optionally substituted with one or more F or Cl; C_3 - C_7 cycloalkyl- C_1 - C_7 alkyl; straight chained or branched C_2 -
15 C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl; phenyl or C_1 - C_6 phenylalkyl; wherein the phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F, Cl, $-\text{CN}$, $-\text{NO}_2$, $-\text{NR}_5\text{R}_6$, $-\text{SO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{COR}_7$, $-(\text{CH}_2)_n\text{OR}_5$, $-(\text{CH}_2)_n\text{CONR}_5\text{R}_6$, $-(\text{CH}_2)_n\text{NR}_5\text{COR}_5$, $-(\text{CH}_2)_n\text{CO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{SO}_2\text{NR}_5\text{R}_6$, straight
20 chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

or R_{12} and R_{13} together with the amide linkage to which they are attached are pyrrolidinonyl, piperidonyl, or
25 oxazolidinonyl;

wherein R_{14} is H; straight chained or branched C_1 - C_4 alkyl; F; or $-(\text{CH}_2)_x\text{OR}_5$;

30 wherein R_{15} is H, straight chained or branched C_1 - C_4 alkyl, or F;

with the proviso that when R_{14} is -OH, R_{15} cannot be F;

wherein R_{16} is perfluoroalkyl, unsubstituted straight
 5 chained or branched C_1 - C_7 alkyl, substituted straight
 chained or branched C_2 - C_7 alkyl, wherein the C_2 - C_7 alkyl may
 be substituted with one or more of F, Cl, -CN, -
 SO_2R_5 , $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, -
 $(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nOCF_3$, perfluoroalkyl,
 10 polyfluoroalkyl, or aminoalkyl, straight chained or
 branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or
 cycloalkenyl; C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl,
 heteroaryl, or C_1 - C_7 phenylalkyl, wherein the phenyl,
 heteroaryl, or C_1 - C_7 phenylalkyl may be substituted with
 15 one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, -
 $(CH_2)_nNR_5COR_5$, -SO₂R₅, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, -
 $(CH_2)_nCONR_5R_6$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, ethylenedioxy,
 methylenedioxy, straight chained or branched C_1 - C_7 alkyl,
 perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight
 20 chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7
 cycloalkyl or cycloalkenyl; quinoliny, 1-naphthyl, 2-
 naphthyl, or 2,1,3-benzothiadiazolyl; wherein the
 quinoliny, 1-naphthyl, 2-naphthyl or 2,1,3-
 benzothiadiazolyl may be substituted with one or more of
 25 F, Cl, Br, -CN, -NO₂, -NR₅R₆, $-(CH_2)_nNR_5COR_5$, -SO₂R₅, -
 $(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nCO_2R_5$, -
 $(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight
 chained or branched C_1 - C_7 alkyl, perfluoroalkyl,
 polyfluoroalkyl, or aminoalkyl;

30

with the proviso that when R_8 is NR₉(R₁₄R₁₅)_sNR₁₀R₁₁, R_{16}
 cannot be quinoliny;

wherein R_{17} is H, straight chained or branched C_1 - C_4 alkyl, perfluoroalkyl, or polyfluoroalkyl;

wherein R_{19} is $-(CH_2)_uOR_5$, $-NR_5R_6$, phenyl, or heteroaryl,
5 wherein the phenyl or heteroaryl may be substituted with one or more of F, Cl, Br, $-CN$, $-NO_2$, $-NR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight chained or branched C_1 - C_7 alkyl,
10 perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl;

wherein m is 0 or 1;

15 wherein each p independently is an integer from 0 to 2 inclusive;

wherein each r independently is an integer from 0 to 3
20 inclusive;

wherein each s independently is an integer from 1 to 6 inclusive;

25 wherein t is an integer from 1 to 4 inclusive;

wherein each u independently is an integer from 2 to 4 inclusive;

30 wherein v is 1 or 2;

with the proviso that when v is 2, m is 0;

wherein z is an integer from 2 to 7;

or a pharmaceutically acceptable salt thereof.

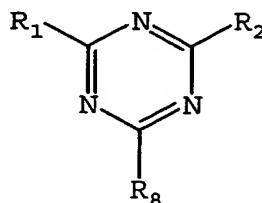
5 The invention also provides a pharmaceutical composition comprising a therapeutically effective amount of the compound of the invention and a pharmaceutically acceptable carrier. This invention further provides a pharmaceutical composition made by combining a therapeutically effective amount of the compound of this
10 invention and a pharmaceutically acceptable carrier. This invention further provides a process for making a pharmaceutical composition comprising combining a therapeutically effective amount of the compound of the invention and a pharmaceutically acceptable carrier.

Brief Description Of The Figures**Figures 1A-1F**

5 Structures of compounds described herein within the
Experimental Details section in Examples 1-58.

Detailed Description Of The Invention

This invention provides a compound having the structure



5

wherein R_1 is F; Cl; Br; I; NR_3R_4 ; or phenyl or heteroaryl; wherein the phenyl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -NR₅R₆, -SO₂R₅, - (CH₂)_nC(Y)R₇, - (CH₂)_nYR₅, - (CH₂)_nC(Y)NR₅R₆, - (CH₂)_nNR₅C(Y)R₅, - (CH₂)_nCO₂R₅, - (CH₂)_nSO₂NR₅R₆, a straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, C₂-C₇ alkenyl or C₂-C₇ alkynyl, or a C₃-C₇ cycloalkyl or cycloalkenyl;

10

15

wherein R_2 is NR_3R_4 ;

wherein R_3 is independently H; - (CH₂)_uYR₅; - (CH₂)_tC(Y)NR₅R₆; - (CH₂)_uNR₅C(Y)R₅; - (CH₂)_tC(Y)R₇; - (CH₂)_tCO₂R₅; - (CH₂)_uNR₅R₆; - (CH₂)_uCN; -C(Y)R₅; -C(Y)NR₅R₆; -CO₂R₅; straight chained or branched C₁-C₇ alkyl, C₂-C₇ alkenyl, or C₂-C₇ alkynyl; C₃-C₇ cycloalkyl or cycloalkenyl; phenyl; C₁-C₆ phenylalkyl; or C₁-C₆ heteroarylalkyl; wherein the phenyl, C₁-C₆ phenylalkyl, or C₁-C₆ heteroarylalkyl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -NR₅R₆, -SO₂R₅, - (CH₂)_nC(Y)R₇, - (CH₂)_nYR₅, - (CH₂)_nC(Y)NR₅R₆, - (CH₂)_nNR₅C(Y)R₅, - (CH₂)_nCO₂R₅, - (CH₂)_nSO₂NR₅R₆, a straight chained or branched C₁-C₇ alkyl, monofluoroalkyl,

20

25

polyfluoroalkyl, aminoalkyl, C₂-C₇ alkenyl or C₂-C₇ alkynyl, or a C₃-C₇ cycloalkyl or cycloalkenyl;

wherein R₄ is independently H; - (CH₂)_uYR₅; -
 5 (CH₂)_tC(Y)NR₅R₆; - (CH₂)_uNR₅C(Y)R₅; - (CH₂)_tC(Y)R₇; -
 (CH₂)_tCO₂R₅; - (CH₂)_uNR₅R₆; - (CH₂)_uCN; straight chained or
 branched C₁-C₇ alkyl; straight chained or branched C₂-C₇
 alkenyl or C₂-C₇ alkynyl; C₃-C₇ cycloalkyl or cycloalkenyl;
 phenyl; or C₁-C₆ phenylalkyl; wherein the phenyl or C₁-C₆
 10 phenylalkyl may be substituted with one or more of F, Cl,
 Br, I, -CN, -NO₂, -NR₅R₆, -SO₂R₅, - (CH₂)_nC(Y)R₇, -
 (CH₂)_nYR₅, - (CH₂)_nC(Y)NR₅R₆, - (CH₂)_nNR₅C(Y)R₅, - (CH₂)_nCO₂R₅,
 - (CH₂)_nSO₂NR₅R₆, a straight chained or branched C₁-C₇ alkyl,
 monofluoroalkyl, polyfluoroalkyl, aminoalkyl, C₂-C₇
 15 alkenyl or C₂-C₇ alkynyl, or a C₃-C₇ cycloalkyl or
 cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to
 which they are attached are 1-azetidiny, 1-
 20 pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl, wherein
 the 1-azetidiny, 1-pyrrolidinyl, 1-piperidinyl, or
 1H-azepanyl is substituted with one or more of F,
 -CN, - (CH₂)_nNR₅R₆, -SO₂R₅, - (CH₂)_nC(Y)R₇, - (CH₂)_nYR₅,
 - (CH₂)_nC(Y)NR₅R₆, - (CH₂)_nNR₅C(Y)R₅, - (CH₂)_nCO₂R₅, a straight
 25 chained or branched C₁-C₇ alkyl, monofluoroalkyl,
 polyfluoroalkyl, aminoalkyl, a C₂-C₇ alkenyl or C₂-C₇
 alkynyl, a C₃-C₇ cycloalkyl or cycloalkenyl, or phenyl or
 heteroaryl; wherein if - (CH₂)_nNR₅R₆, - (CH₂)_nYR₅, or -
 (CH₂)_nNR₅C(Y)R₅ are in the 2-position, then n is not 0;
 30 wherein the phenyl or heteroaryl may be substituted with
 one or more of F, Cl, Br, I, -CN, -NO₂, -NR₅R₆, -
 SO₂R₅, - (CH₂)_nC(Y)R₇, - (CH₂)_nYR₅, - (CH₂)_nC(Y)NR₅R₆, -
 (CH₂)_nNR₅C(Y)R₅, - (CH₂)_nCO₂R₅, - (CH₂)_nSO₂NR₅R₆, a straight
 chained or branched C₁-C₇ alkyl, monofluoroalkyl,

polyfluoroalkyl, aminoalkyl, a C₂-C₇ alkenyl or C₂-C₇ alkynyl, or a C₃-C₇ cycloalkyl or cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to which they are attached are morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl, wherein the morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl is substituted with one or more straight chained or branched C₁-C₇ alkyl or C₁-C₇ phenylalkyl; and wherein the nitrogen atom of the piperazinyl or [1,4]diazepanyl ring is substituted with - (CH₂)_uYR₅; - (CH₂)_tC(Y)NR₅R₆; - (CH₂)_uNR₅C(Y)R₅; - (CH₂)_tC(Y)R₇; - (CH₂)_tCO₂R₅; - (CH₂)_uNR₅R₆; - (CH₂)_uCN; - C(Y)R₅; - C(Y)NR₅R₆; - CO₂R₅; straight chained or branched C₁-C₇ alkyl, C₂-C₇ alkenyl, or C₂-C₇ alkynyl; or C₃-C₇ cycloalkyl or cycloalkenyl; phenyl; C₁-C₆ phenylalkyl; or C₁-C₆ heteroarylalkyl; wherein the phenyl, C₁-C₆ phenylalkyl, or C₁-C₆ heteroarylalkyl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -NR₅R₆, -SO₂R₅, - (CH₂)_nC(Y)R₇, - (CH₂)_nYR₅, - (CH₂)_nC(Y)NR₅R₆, - (CH₂)_nNR₅C(Y)R₅, - (CH₂)_nCO₂R₅, - (CH₂)_nSO₂NR₅R₆, a straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, a C₂-C₇ alkenyl or C₂-C₇ alkynyl, or a C₃-C₇ cycloalkyl or cycloalkenyl;

wherein each of R₅, R₆ and R₇ is independently H; or straight chained or branched C₁-C₇ alkyl;

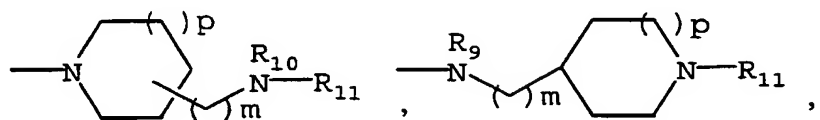
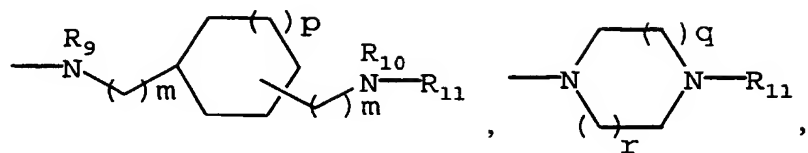
wherein each n is independently an integer from 0 to 6 inclusive;

wherein each t is independently an integer from 1 to 4 inclusive;

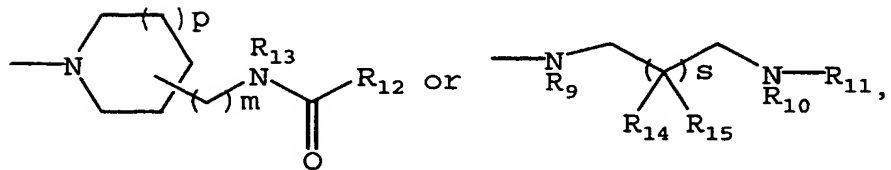
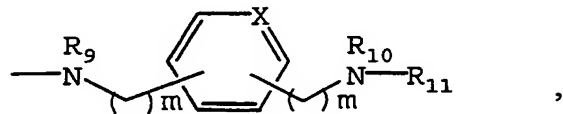
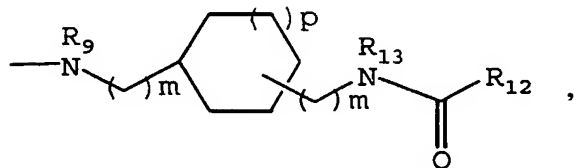
wherein each u is independently an integer from 2 to 4 inclusive;

5 wherein Y is O or S;

wherein R₈ is



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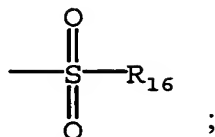
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provided that if R₈ contains a piperidinyl group and m is 0, then the compound is not an -aminal-containing compound;

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wherein each of R_9 and R_{10} is independently H; straight chained or branched C_1 - C_4 alkyl;

5 wherein R_{11} is H or



10 wherein R_{12} is H;

wherein R_{13} is independently H; $-(CH_2)_uYR_5$; $-(CH_2)_tC(Y)NR_5R_6$; $-(CH_2)_uNR_5C(Y)R_5$; $-(CH_2)_tC(Y)R_7$; $-(CH_2)_tCO_2R_5$; $-(CH_2)_uNR_5R_6$; $-(CH_2)_uCN$; $-C(Y)R_5$; $C(Y)NR_5R_6$; $-CO_2R_5$; straight chained or branched C_1 - C_7 alkyl; C_1 - C_7 alkyl substituted with one or more F or Cl; C_3 - C_7 cycloalkyl- C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl, or alkynyl; or C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl or C_1 - C_6 phenylalkyl; wherein the
 20 phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F, Cl, $-CN$, $-NO_2$, $-NR_5R_6$, $-SO_2R_5$, $-(CH_2)_nC(Y)R_7$, $-(CH_2)_nYR_5$, $-(CH_2)_nC(Y)NR_5R_6$, $-(CH_2)_nNR_5C(Y)R_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, a straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl,
 25 a C_2 - C_7 alkenyl or C_2 - C_7 alkynyl, or a C_3 - C_7 cycloalkyl or cycloalkenyl;

or R_{12} and R_{13} together with the amide linkage to which they are attached are pyrrolidinonyl or piperidonyl;

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wherein R_{14} is H; straight chained or branched C_1 - C_7 alkyl; F; or $-(CH_2)_nOR_5$;

wherein R_{15} is H, straight chained or branched C_1 - C_7 alkyl, or F;

5 wherein R_{16} is NR_3R_4 , unsubstituted straight chained or branched C_2 - C_7 alkyl, substituted straight chained or branched C_1 - C_7 alkyl, wherein the C_1 - C_7 alkyl may be substituted with one or more of F, Cl, -CN, - NR_5R_6 , - SO_2R_5 , - $(CH_2)_nC(Y)R_7$, - $(CH_2)_nYR_5$, - $(CH_2)_nC(Y)NR_5R_6$, - $(CH_2)_nNR_5C(Y)R_5$, - $(CH_2)_nCO_2R_5$, - $(CH_2)_nOCF_3$, monofluoroalkyl, 10 polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or C_2 - C_7 alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl, phenyl, heteroaryl, or C_1 - C_7 phenylalkyl, wherein the phenyl, heteroaryl, or C_1 - C_7 phenylalkyl may be substituted with one or more of F, 15 Cl, Br, I, -CN, - NO_2 , - NR_5R_6 , - $(CH_2)_nNR_5C(Y)R_5$, - SO_2R_5 , - $(CH_2)_nC(Y)R_7$, - $(CH_2)_nYR_5$, - $(CH_2)_nC(Y)NR_5R_6$, - $(CH_2)_nCO_2R_5$, - $(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight 20 chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl; quinolinyl, 1-naphthyl, 2-naphthyl, or 2,1,3-benzothiadiazolyl; with the provisos that when R_1 is F, Cl, Br, or I, then R_{16} is 1-naphthyl; and when R_1 and R_2 are morpholinyl, then R_{16} is 25 not NR_3R_4 ;

wherein each m is independently an integer from 0 to 3 inclusive;

30 wherein each s is independently an integer from 1 to 6 inclusive;

wherein each p is independently an integer from 0 to 2 inclusive;

wherein each q is independently an integer from 1 to 2 inclusive;

5 wherein each r is independently an integer from 1 to 2 inclusive;

wherein X is N or C;

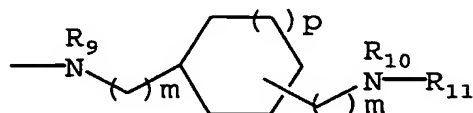
10 or a pharmaceutically acceptable salt thereof.

An α -aminal-containing compound is a compound in which a nitrogen is directly attached to the α -carbon of the
15 piperidinyl group.

In one embodiment, the compound of this invention comprises the (+) enantiomer. In another embodiment, the compound comprises the (-) enantiomer.

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In one embodiment, R_8 is



In another embodiment, R_1 is F, Cl, Br, I, or NR_3R_4 .

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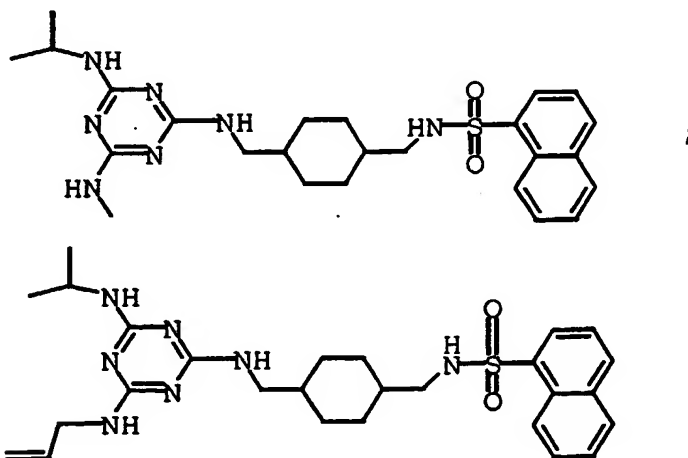
In another embodiment, R_1 and R_2 are both NR_3R_4 where R_3 and R_4 are independently H; straight chained or branched C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or R_3 and R_4 taken together with the nitrogen atom to which they are attached are morpholinyl, piperazinyl,
30 or 1-pyrrolidinyl, wherein the morpholinyl, piperazinyl, or 1-pyrrolidinyl is substituted with one

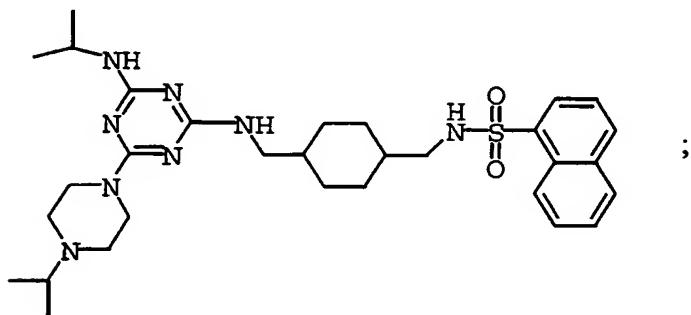
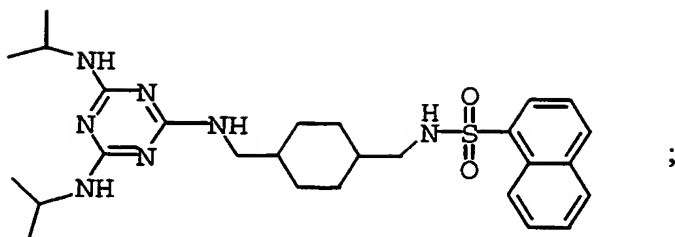
or more straight chained or branched C₁-C₇ alkyl or C₁-C₇ phenylalkyl; and wherein the nitrogen atom of the piperazinyl ring is substituted with H; -(CH₂)_uYR₅; -(CH₂)_tC(Y)NR₅R₆; -(CH₂)_uNR₅C(Y)R₅; -(CH₂)_tC(Y)R₇; -(CH₂)_tCO₂R₅; -(CH₂)_uNR₅R₆; -(CH₂)_uCN; -C(Y)R₅; -C(Y)NR₅R₆; -CO₂R₅; straight chained or branched C₁-C₇ alkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl or cycloalkenyl; phenyl; C₁-C₆ phenylalkyl; or C₁-C₆ heteroarylalkyl.

In another embodiment, R₁₆ is phenyl, 1-naphthyl, quinolinyl, or 2,1,3-benzothiadiazolyl; wherein the phenyl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -NR₅R₆, -(CH₂)_nNR₅C(Y)R₅, -SO₂R₅, -(CH₂)_nC(Y)R₇, -(CH₂)_nYR₅, -(CH₂)_nC(Y)NR₅R₆, -(CH₂)_nCO₂R₅, -(CH₂)_nSO₂NR₅R₆, ethylenedioxy, methylenedioxy, straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl.

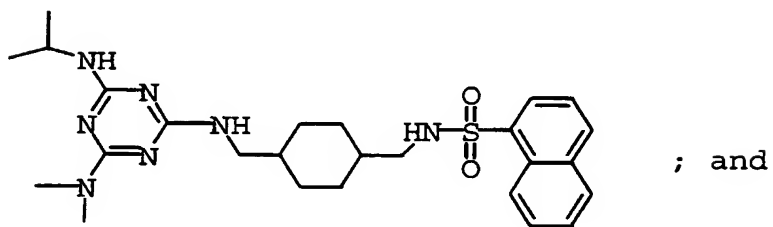
In another embodiment, R₉ is H, R₁₀ is H, p is 1, and m is 1.

In a presently preferred embodiment, the compound is selected from the group consisting of:

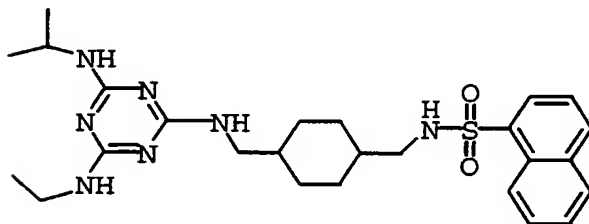




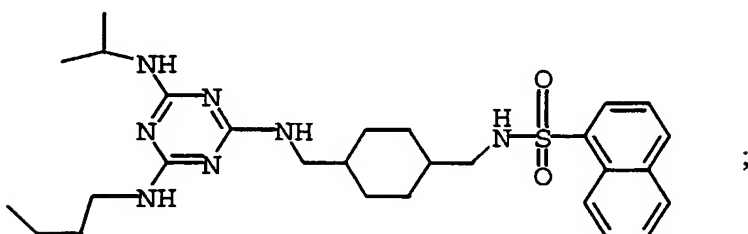
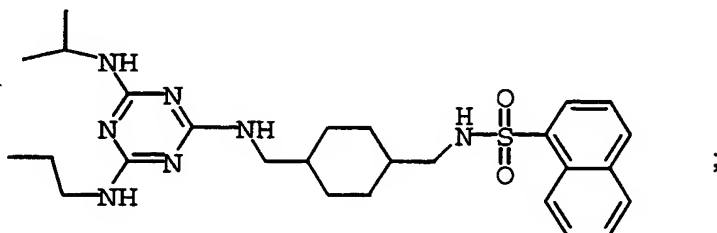
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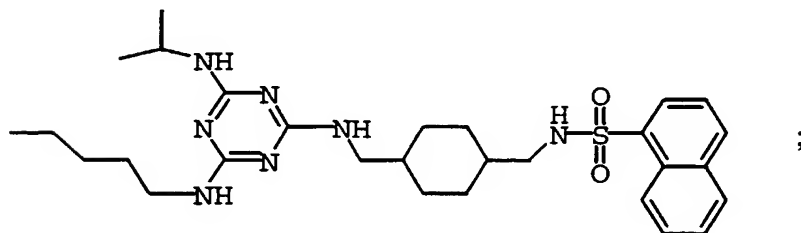
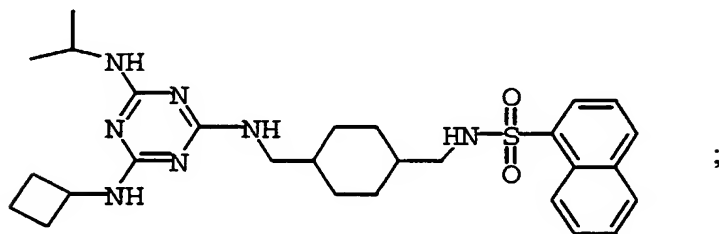
; and



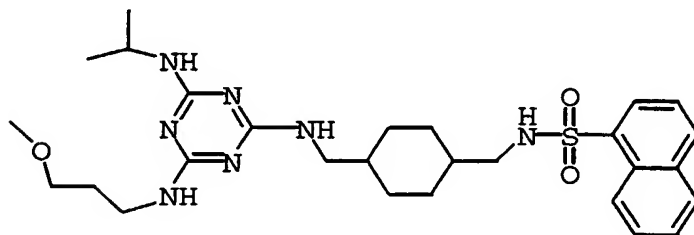
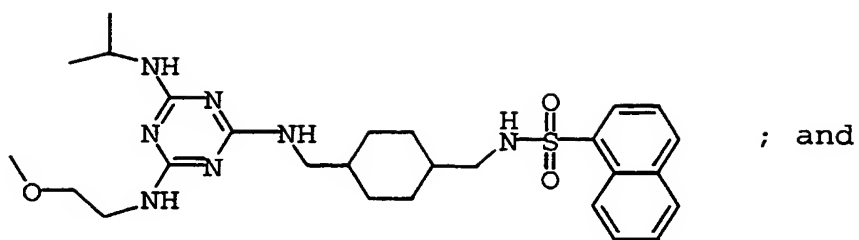
In another presently preferred embodiment, the compound is selected from the group consisting of:



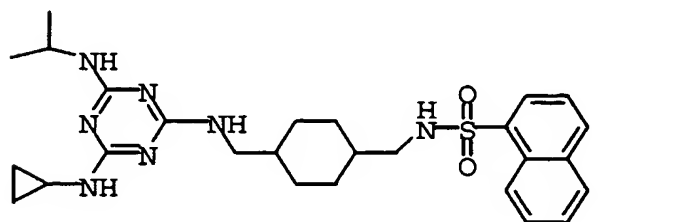
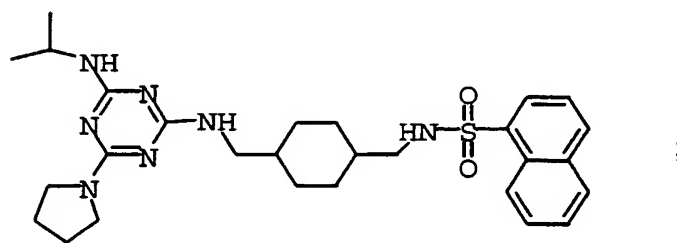
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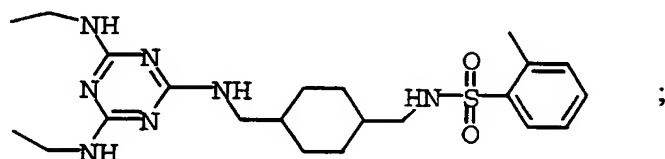
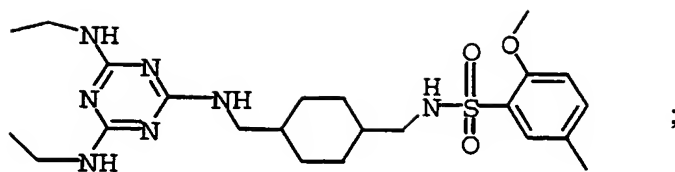


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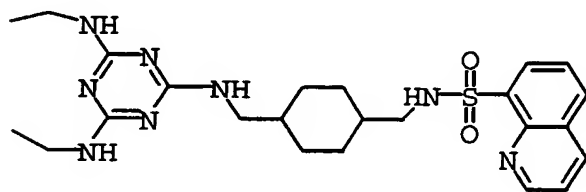
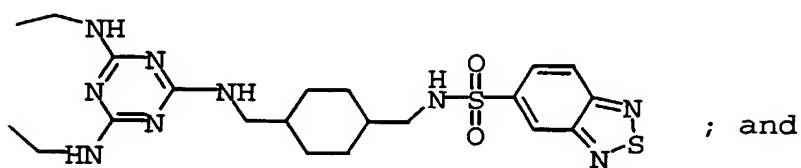
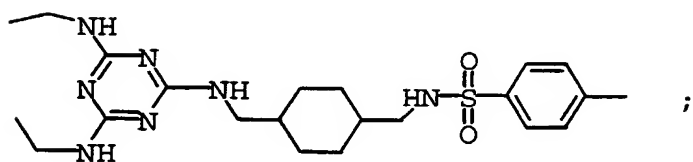


- 5 In a further presently preferred embodiment, the compound is selected from the group consisting of:





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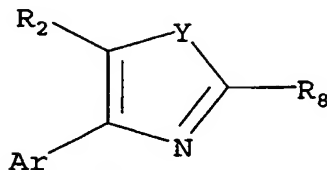


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In the present invention as relates to triazine compounds, the term "heteroaryl" is used to mean and include five and six membered aromatic rings that may contain one or more

heteroatoms such as oxygen, sulfur, nitrogen. Heteroaryl groups include, but are not limited to, pyrazolyl (preferably 1-pyrazolyl), pyrrolyl, furanyl, pyridyl (preferably 2-pyridyl or 3-pyridyl), imidazolyl (preferably 1-imidazolyl), oxazolyl, pyrimidinyl, isoxazolyl, and thienyl.

The invention provides a compound having the structure:



wherein Y is O, S or NH;

5

wherein Ar is a heteroaryl ring that may be optionally substituted with one or more R₁ groups;

10

wherein each R₁ independently is H, F, Cl, Br, -CN, -OH, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, -SO₂C₆H₅, -SO₂NR₅R₆, -C₆H₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, ethylenedioxy, methylenedioxy, perfluoroalkyl, polyfluoroalkyl, aminoalkyl, or straight chained or branched C₁-C₇ alkyl; or phenyl, heteroaryl, or C₁-C₇ phenylalkyl, wherein the phenyl, heteroaryl, or C₁-C₇ phenylalkyl may be substituted with one or more of F, Cl, Br, -CF₃, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, or straight chained or branched C₁-C₄ alkyl;

15

20

wherein R₂ is H, straight chained or branched C₁-C₄ alkyl, -(CH₂)_tOR₅, phenyl optionally substituted with one or more of F, Cl, Br, -CF₃, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, or straight chained or branched C₁-C₄ alkyl;

25

wherein R₅ is independently H; or straight chained or branched C₁-C₇ alkyl;

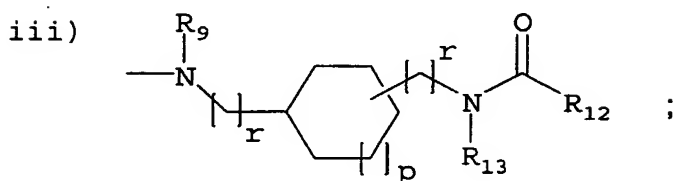
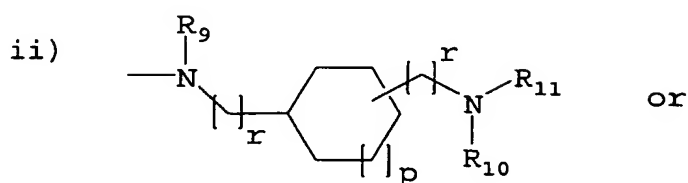
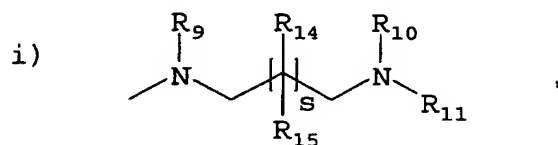
wherein R₆ is independently H; or straight chained or branched C₁-C₇ alkyl;

30

wherein each n independently is an integer from 0 to 6 inclusive;

wherein R_8 is

5



provided that when R_8 is (iii), and Ar is thiazol-2-yl, R_1 cannot be H;

10

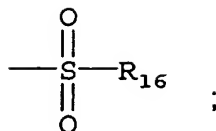
wherein R_9 is independently H; or straight chained or branched C_1 - C_4 alkyl;

wherein R_{10} is independently H; or straight chained or branched C_1 - C_4 alkyl;

15

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wherein R_{11} is



5

wherein R_{12} is H, straight chained or branched C_1 - C_7 alkyl;
or $(\text{CH}_2)_n\text{OR}_{17}$;

10 wherein R_{13} is independently $-(\text{CH}_2)_u\text{OR}_5$; $-(\text{CH}_2)_t\text{CONR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{NR}_5\text{COR}_5$; $-(\text{CH}_2)_t\text{COR}_7$; $-(\text{CH}_2)_t\text{CO}_2\text{R}_5$; $-(\text{CH}_2)_u\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{CN}$; straight chained or branched C_1 - C_7 alkyl; C_1 - C_7 alkyl in which the C_2 - C_7 atoms may be optionally substituted with one or more F or Cl; C_3 - C_7 cycloalkyl- C_1 - C_7 alkyl; straight chained or branched C_2 -
15 C_7 alkenyl; or C_3 - C_5 cycloalkyl;

or R_{12} and R_{13} together with the amide linkage to which they are attached are pyrrolidinonyl, piperidonyl, or oxazolidinonyl;

20

wherein R_7 is independently straight chained or branched C_1 - C_7 alkyl;

25

wherein R_{14} is H; straight chained or branched C_1 - C_4 alkyl; F; or $-(\text{CH}_2)_r\text{OR}_5$;

wherein R_{15} is H, straight chained or branched C_1 - C_4 alkyl, or F;

30

with the proviso that when R_{14} is -OH, R_{15} cannot be F;

wherein R_{16} is $-NR_3R_4$, perfluoroalkyl, unsubstituted straight chained or branched C_2-C_7 alkyl, substituted straight chained or branched C_2-C_7 alkyl, wherein the C_2-C_7 alkyl may be substituted with one or more of F, Cl, -CN, $-NR_5R_6$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nOCF_3$, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, or C_3-C_7 cycloalkyl; C_3-C_7 cycloalkyl; phenyl, thienyl, isoxazolyl, quinolinyl, or C_1-C_7 phenylalkyl, wherein the phenyl, thienyl, isoxazolyl, quinolinyl, or C_1-C_7 phenylalkyl may be substituted with one or more of F, Cl, Br, I, -CN, $-NO_2$, $-NR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight chained or branched C_1-C_3 alkyl, perfluoroalkyl, or aminoalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, or C_3-C_7 cycloalkyl or cycloalkenyl; quinolinyl, 1-naphthyl, 2-naphthyl, or 2,1,3-benzothiadiazolyl; wherein the quinolinyl, 1-naphthyl, 2-naphthyl or 2,1,3-benzothiadiazolyl may be substituted with one or more of F, Cl, Br, -CN, $-NO_2$, $-NR_5R_6$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, straight chained or branched C_1-C_4 alkyl, perfluoroalkyl, or aminoalkyl;

25

provided that when R_{16} is quinolinyl and R_8 is (ii), Ar cannot be pyrrolyl;

30

provided that when R_{16} is $N(CH_3)_2$ and R_8 is (i), Ar cannot be thiazol-2-yl;

wherein R_3 is independently H; $-(CH_2)_uOR_5$; $-(CH_2)_tCONR_5R_6$; $-(CH_2)_uNR_5COR_5$; $-(CH_2)_tCOR_7$; $-(CH_2)_tCO_2R_5$; $-(CH_2)_uNR_5R_6$; $-(CH_2)_uCN$; straight chained or

branched C₁-C₇ alkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; or C₃-C₇ cycloalkyl or cycloalkenyl; phenyl, or C₁-C₆ phenylalkyl; wherein the phenyl, or C₁-C₆ phenylalkyl may be substituted with one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nCOR₇, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, -(CH₂)_nCO₂R₅, -(CH₂)_nSO₂NR₅R₆, straight chained or branched C₁-C₇ alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl;

wherein R₄ is independently H; -(CH₂)_uOR₅; -(CH₂)_tCONR₅R₆; -(CH₂)_uNR₅COR₅; -(CH₂)_tCOR₇; -(CH₂)_tCO₂R₅; -(CH₂)_uNR₅R₆; -(CH₂)_uCN; straight chained or branched C₁-C₇ alkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; or C₃-C₇ cycloalkyl or cycloalkenyl; phenyl or C₁-C₆ phenylalkyl; wherein the phenyl or C₁-C₆ phenylalkyl may be substituted with one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nCOR₇, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, -(CH₂)_nCO₂R₅, -(CH₂)_nSO₂NR₅R₆, straight chained or branched C₁-C₇ alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to which they are attached are 1-azetidiny, 1-pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl, wherein the 1-azetidiny, 1-pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl is substituted with one or more of F, -CN, -(CH₂)_nNR₅R₆, -SO₂R₅, -(CH₂)_nCOR₇, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, -(CH₂)_nCO₂R₅, straight chained or branched C₁-C₇ alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇

cycloalkyl or cycloalkenyl, or phenyl or thienyl, or isoxazolyl, or quinolinyl; wherein if $-(CH_2)_nNR_5R_6$, $-(CH_2)_nOR_5$, or $-(CH_2)_nNR_5COR_5$ are in the 2-position, then n is not 0; wherein the phenyl, thienyl, isoxazolyl, or quinolinyl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -NR₅R₆, -SO₂R₅, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, straight chained or branched C₁-C₇ alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C₂-C₇ alkenyl or alkynyl, or C₃-C₇ cycloalkyl or cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to which they are attached are morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl, wherein the morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl is optionally substituted with straight chained or branched C₁-C₅ alkyl or $-(CH_2)_tOR_5$; and wherein the nitrogen atom of the piperazinyl or [1,4]diazepanyl ring may be optionally substituted with $-(CH_2)_uOR_5$; -COR₅; straight chained or branched C₁-C₅ alkyl; or phenyl; wherein the phenyl may be substituted with one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, $-(CH_2)_nOR_5$, straight chained or branched C₁-C₃ alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

wherein R₁₇ is straight chained or branched C₁-C₄ alkyl, perfluoroalkyl, or polyfluoroalkyl;

30

wherein each p independently is an integer from 0 to 2 inclusive;

46

wherein each r independently is an integer from 0 to 3 inclusive;

5 wherein each s independently is an integer from 3 to 6 inclusive;

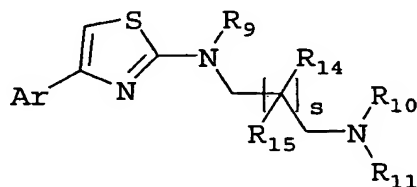
wherein t is an integer from 1 to 4 inclusive;

10 wherein each u independently is an integer from 2 to 4 inclusive;

or a pharmaceutically acceptable salt thereof.

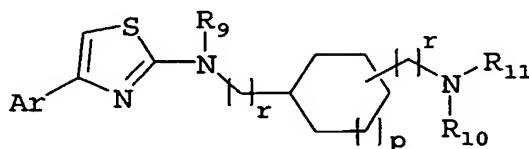
15 In one embodiment, the compound comprises the (+) enantiomer. In another embodiment, the compound comprises the (-) enantiomer.

In one embodiment, the compound has the structure:



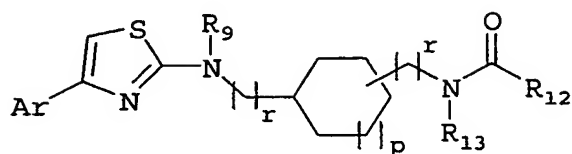
20

In another embodiment, the compound has the structure:



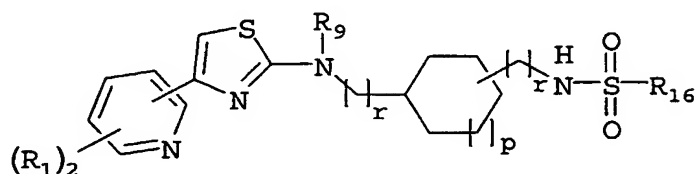
25

In still another embodiment, the compound has the structure:



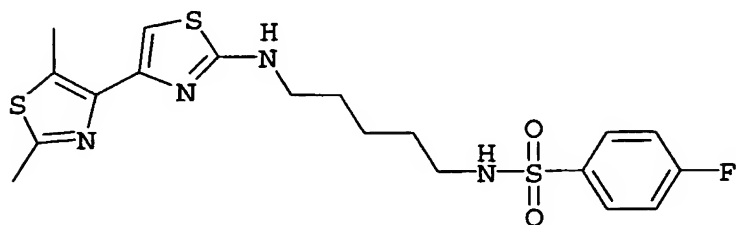
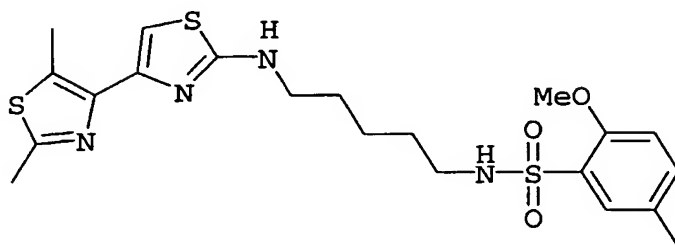
5

In a further embodiment, the compound has the structure:



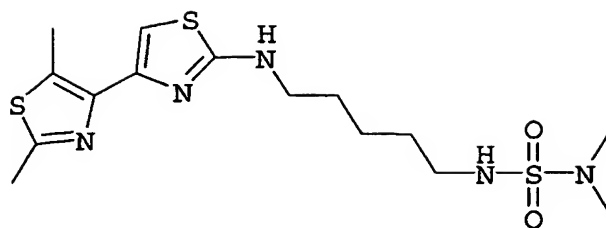
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In still further embodiments, the compound has the structure selected from the group consisting of:

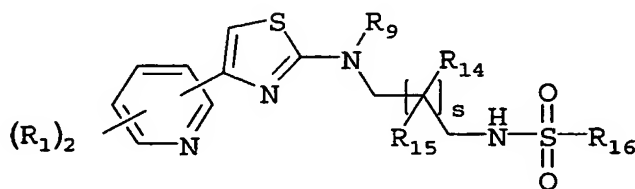


and

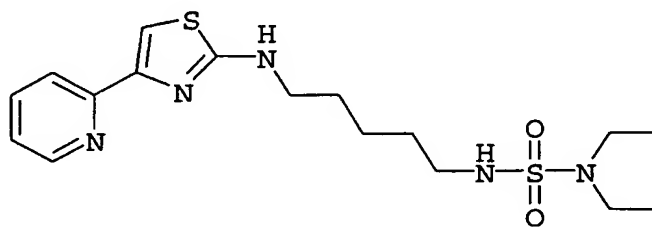
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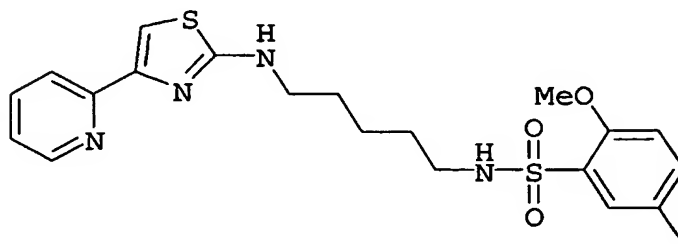
5 In another embodiment, the compound has the structure:



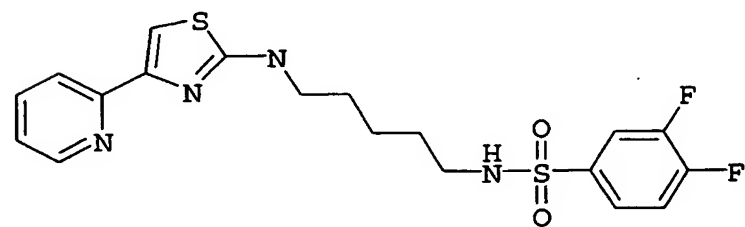
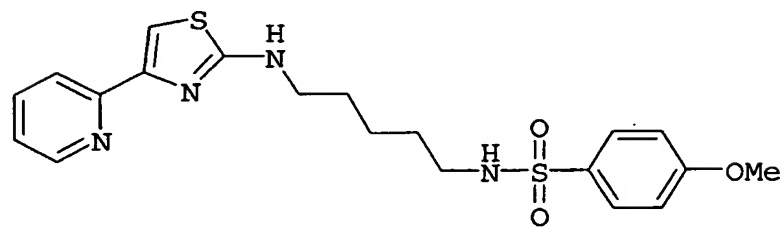
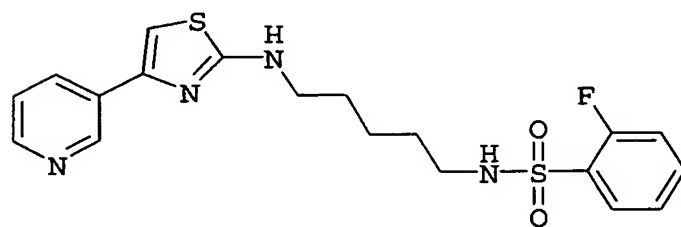
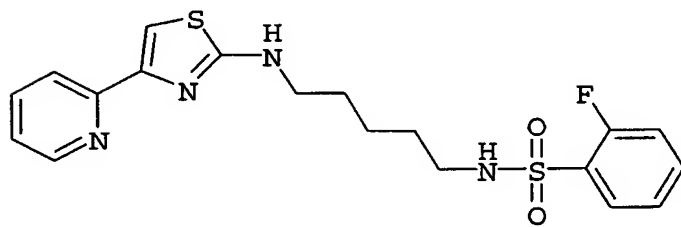
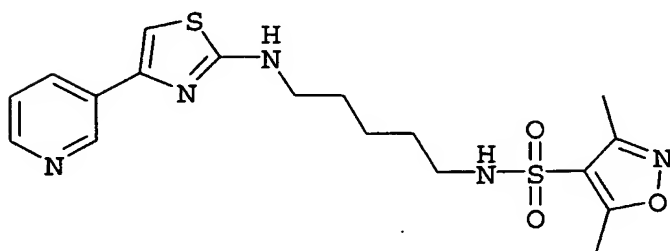
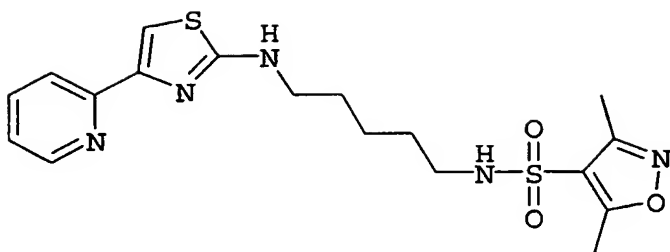
In further embodiments, the compound has the structure selected from the group consisting of:



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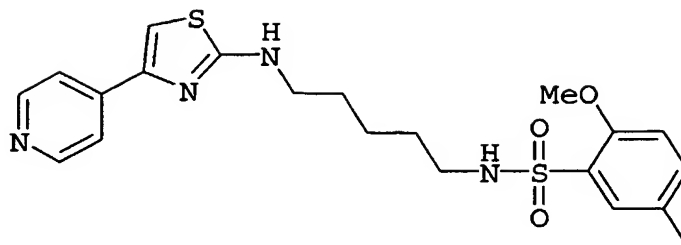


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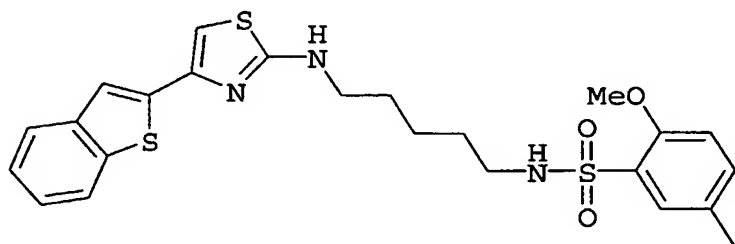
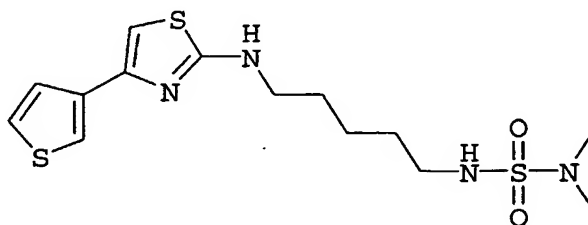


and

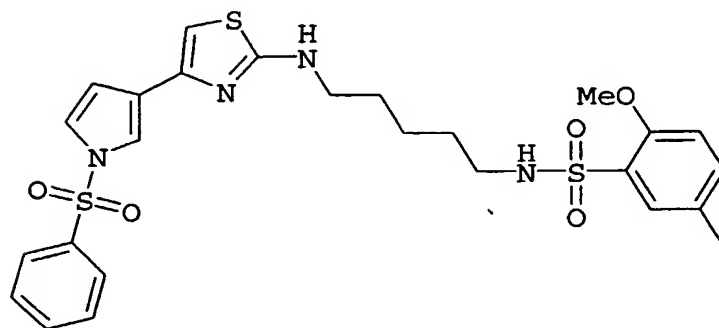
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In still other embodiments, the compound has the structure selected from the group consisting of:



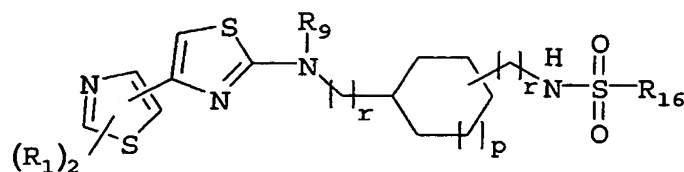
and



5

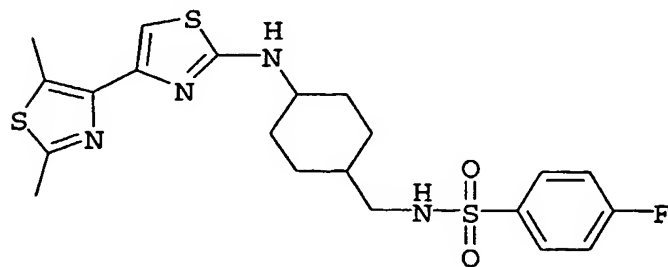
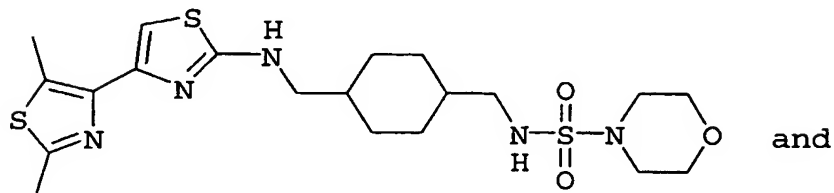
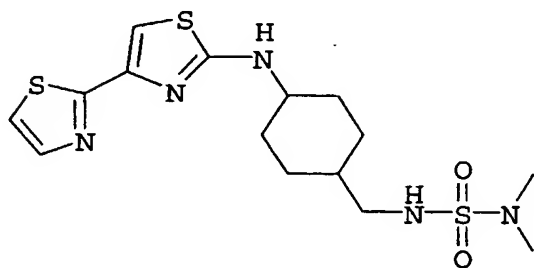
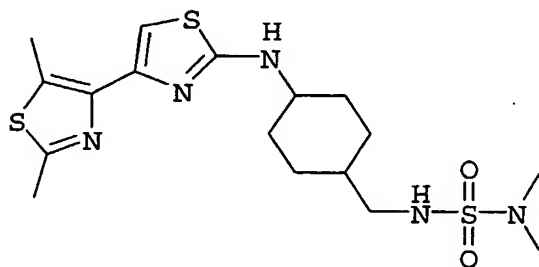
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In a further embodiment, the compound has the structure:

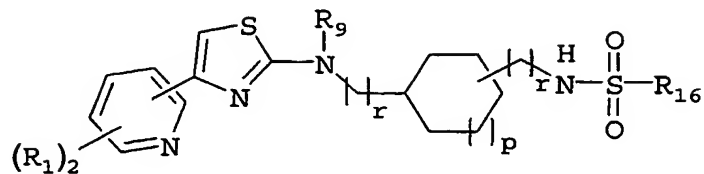


5

In still further embodiments, the compound has the structure selected from the group consisting of:

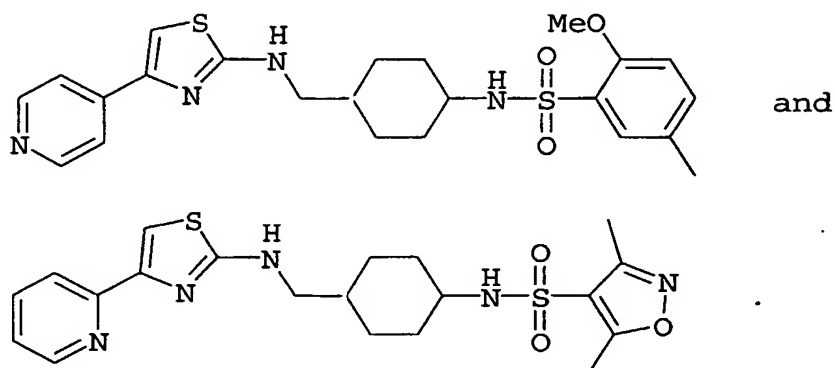


In another embodiment, the compound has the structure:



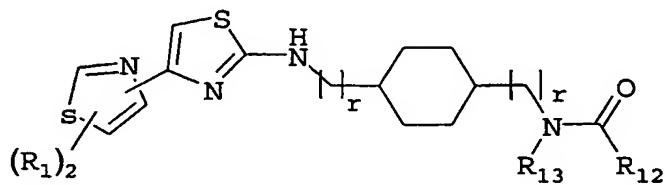
5

In still other embodiments, the compound has the structure selected from the group consisting of:



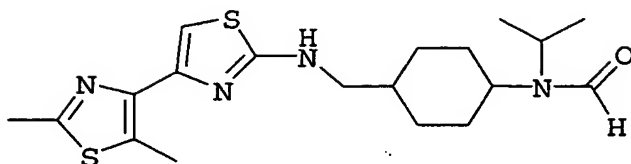
10

In a further embodiment, the compound has the structure:



15

In still a further embodiment, the compound has the structure:



5

In the present invention as relates to bicyclic compounds, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one sulfur or nitrogen atom or one or more oxygen, sulfur, or nitrogen atoms. Examples of heteroaryl groups include, but are not limited to, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl. In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indolizinyl, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, imidazo[2,1-b]thiazolyl, quinolinyl, isoquinolinyl, quinolizinyl, and 2,1,3-benzothiazolyl.

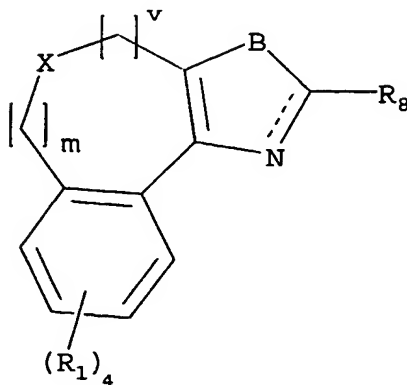
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The invention provides a compound having the structure:



wherein each R_1 is independently H, F, Cl, Br, -CN, -OH,
 5 -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, -
 (CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, perfluoroalkyl,
 polyfluoroalkyl, aminoalkyl, or straight chained or
 branched C₁-C₇ alkyl;

10 wherein R₅ is independently H; or straight chained or
 branched C₁-C₇ alkyl;

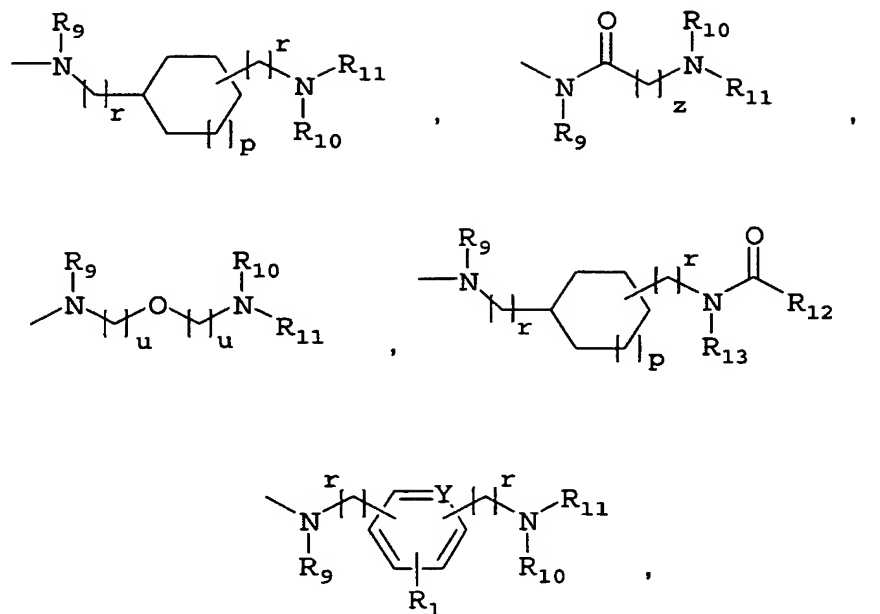
wherein R₆ is independently H; or straight chained or
 branched C₁-C₇ alkyl;

15 wherein B is O, NH or S;

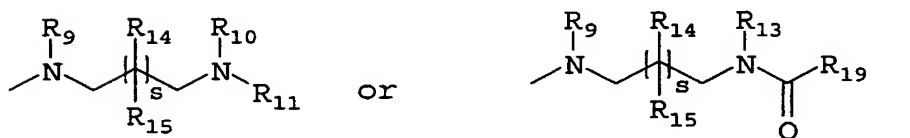
wherein X is S, SO or SO₂;

20 wherein each n independently is an integer from 0 to 6
 inclusive;

wherein R_8 is



5



wherein Y is C or N;

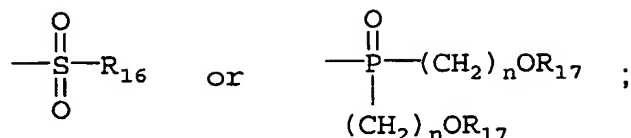
10 wherein R_7 is independently straight chained or branched C_1 - C_7 alkyl;

wherein R_9 is independently H; or straight chained or branched C_1 - C_4 alkyl;

15

wherein R_{10} is independently H; or straight chained or branched C_1 - C_4 alkyl;

wherein R_{11} is



5 wherein R_{12} is H, straight chained or branched C_1 - C_7 alkyl, $(\text{CH}_2)_u\text{OR}_{17}$, or $\text{O}(\text{CH}_2)_u\text{OR}_{17}$; provided that when X is O, R_{12} cannot be methyl;

10 wherein R_{13} is independently H; $-(\text{CH}_2)_u\text{OR}_5$; $-(\text{CH}_2)_t\text{CONR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{NR}_5\text{COR}_5$; $-(\text{CH}_2)_t\text{COR}_7$; $-(\text{CH}_2)_t\text{CO}_2\text{R}_5$; $-(\text{CH}_2)_u\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{CN}$; straight chained or branched C_1 - C_7 alkyl; C_1 - C_7 alkyl in which the C_2 - C_7 atoms may be optionally substituted with one or more F or Cl; C_3 - C_7 cycloalkyl- C_1 - C_7 alkyl; straight chained or branched C_2 -
15 C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl; phenyl or C_1 - C_6 phenylalkyl; wherein the phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F, Cl, $-\text{CN}$, $-\text{NO}_2$, $-\text{NR}_5\text{R}_6$, $-\text{SO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{COR}_7$, $-(\text{CH}_2)_n\text{OR}_5$, $-(\text{CH}_2)_n\text{CONR}_5\text{R}_6$, $-(\text{CH}_2)_n\text{NR}_5\text{COR}_5$, $-(\text{CH}_2)_n\text{CO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{SO}_2\text{NR}_5\text{R}_6$, straight
20 chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

or R_{12} and R_{13} together with the amide linkage to which they are attached are pyrrolidinonyl, piperidonyl, or
25 oxazolidinonyl;

wherein R_{14} is H; straight chained or branched C_1 - C_4 alkyl; F; or $-(\text{CH}_2)_r\text{OR}_5$;

30 wherein R_{15} is H, straight chained or branched C_1 - C_4 alkyl, or F;

with the proviso that when R_{14} is -OH, R_{15} cannot be F;

wherein R_{16} is perfluoroalkyl, unsubstituted straight
5 chained or branched C_1 - C_7 alkyl, substituted straight
chained or branched C_2 - C_7 alkyl, wherein the C_2 - C_7 alkyl may
be substituted with one or more of F, Cl, -CN, -
 SO_2R_5 , $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, -
 $(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nOCF_3$, perfluoroalkyl,
10 polyfluoroalkyl, or aminoalkyl, straight chained or
branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or
cycloalkenyl; C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl,
heteroaryl, or C_1 - C_7 phenylalkyl, wherein the phenyl,
heteroaryl, or C_1 - C_7 phenylalkyl may be substituted with
15 one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆, -
 $(CH_2)_nNR_5COR_5$, -SO₂R₅, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, -
 $(CH_2)_nCONR_5R_6$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, ethylenedioxy,
methylenedioxy, straight chained or branched C_1 - C_7 alkyl,
perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight
20 chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7
cycloalkyl or cycloalkenyl; quinolinyl, 1-naphthyl, 2-
naphthyl, or 2,1,3-benzothiadiazolyl; wherein the
quinolinyl, 1-naphthyl, 2-naphthyl or 2,1,3-
benzothiadiazolyl may be substituted with one or more of
25 F, Cl, Br, -CN, -NO₂, -NR₅R₆, $-(CH_2)_nNR_5COR_5$, -SO₂R₅, -
 $(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nCO_2R_5$, -
 $(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight
chained or branched C_1 - C_7 alkyl, perfluoroalkyl,
polyfluoroalkyl, or aminoalkyl;

30 with the proviso that when R_8 is NR₉(R₁₄R₁₅)_sNR₁₀R₁₁, R_{16}
cannot be quinolinyl;

wherein R_{17} is H, straight chained or branched C_1 - C_4 alkyl, perfluoroalkyl, or polyfluoroalkyl;

wherein R_{19} is $-(CH_2)_uOR_5$, $-NR_5R_6$, phenyl, or heteroaryl,
5 wherein the phenyl or heteroaryl may be substituted with one or more of F, Cl, Br, -CN, $-NO_2$, $-NR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight chained or branched C_1 - C_7 alkyl,
10 perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl;

wherein m is 0 or 1;

15 wherein each p independently is an integer from 0 to 2 inclusive;

wherein each r independently is an integer from 0 to 3
20 inclusive;

wherein each s independently is an integer from 1 to 6 inclusive;

25 wherein t is an integer from 1 to 4 inclusive;

wherein each u independently is an integer from 2 to 4 inclusive;

30 wherein v is 1 or 2;

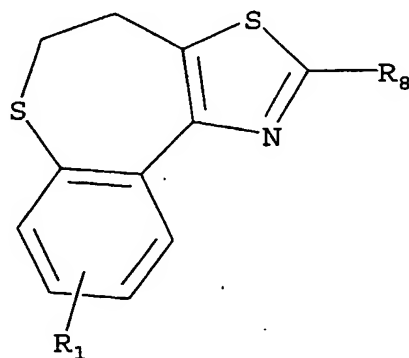
with the proviso that when v is 2, m is 0;

wherein z is an integer from 2 to 7;

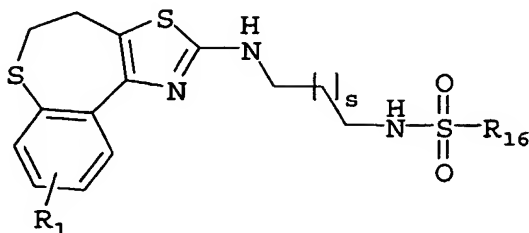
or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound comprises the (+)
5 enantiomer. In another embodiment, the compound comprises
the (-) enantiomer.

In one embodiment, the compound has the structure:

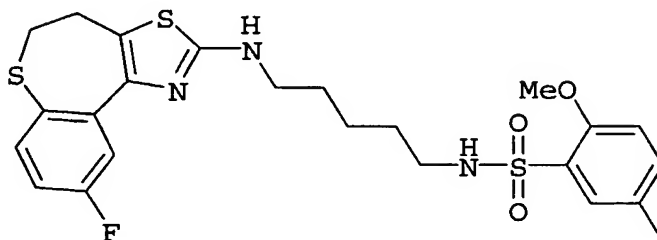


In another embodiment, the compound has the structure:



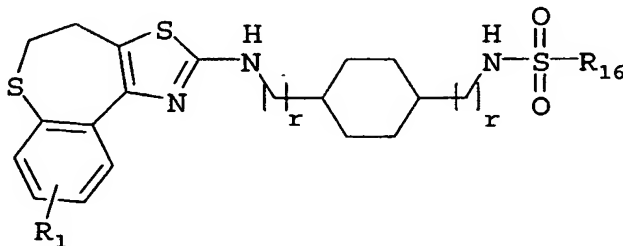
5

In still another embodiment, the compound has the structure:

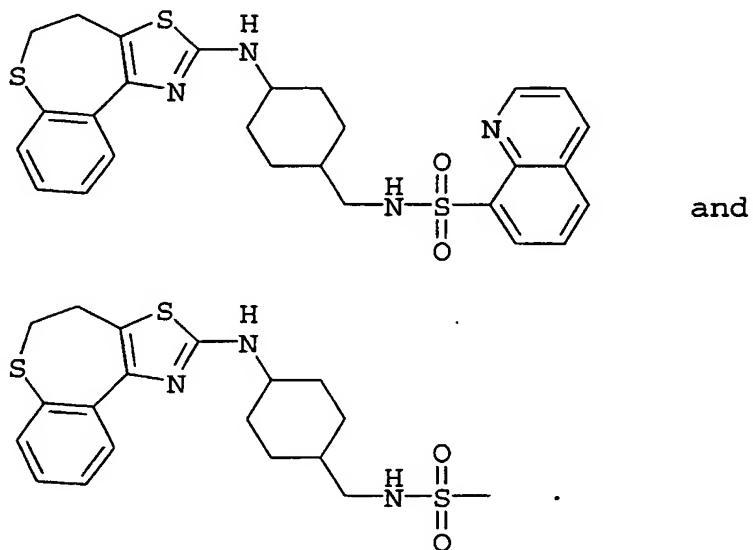


10

In a further embodiment, the compound has the structure:

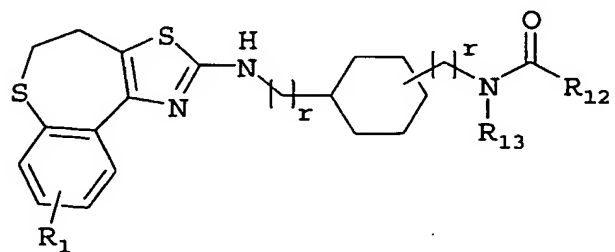


In still further embodiments, the compound has the structure selected from the group consisting of:



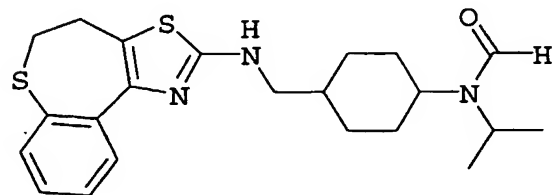
5

In another embodiment, the compound has the structure:



In still another embodiment, the compound has the structure:

10



In the present invention as relates to tricyclic compounds, the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more heteroatoms such as oxygen, sulfur, and nitrogen.

5 Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl. In
10 addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indolizinyll, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl,
15 benzthiazolyl, purinyl, imidazo[2,1-b]thiazolyl, quinolinyl, isoquinolinyl, quinolizinyll, and 2,1,3-benzothiazolyl. Furthermore, any of the heteroaryl groups recited above may be substituted with thienyl, isoxazolyl,
20 or pyridyl.

Included within the scope of this invention are pharmaceutically acceptable salts and complexes of all of the compounds described herein. The salts include but are
25 not limited to the acids and bases listed herein. The salts include, but are not limited to the following inorganic acids: hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and boric acid. The salts include, but are not limited to the following organic
30 acids: acetic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, maleic acid, citric acid, methanesulfonic acid, benzoic acid, glycolic acid, lactic acid and mandelic acid. The salts include, but are not limited to the inorganic base, ammonia. The salts include,

but are not limited to the following organic bases:
methylamine, ethylamine, propylamine, dimethylamine,
diethylamine, trimethylamine, triethylamine,
ethylenediamine, hydroxyethylamine, morpholine, piperazine
5 and guanidine. This invention further provides for the
hydrates and polymorphs of all of the compounds described
herein.

The present invention includes within its scope prodrugs
10 of the compounds of the invention. In general, such
prodrugs will be functional derivatives of the compounds
of the invention which are readily convertible in vivo
into the required compound. Thus, in the present
invention, the term "administering" shall encompass the
15 treatment of the various conditions described with the
compound specifically disclosed or with a compound which
may not be specifically disclosed, but which converts to
the specified compound in vivo after administration to the
patient. Conventional procedures for the selection and
20 preparation of suitable prodrug derivatives are described,
for example, in Design of Prodrugs, ed. H. Bundgaard,
Elsevier, 1985.

The present invention further includes metabolites of the
25 compounds of the present invention. Metabolites include
active species produced upon introduction of compounds of
this invention into the biological milieu.

This invention further provides a pharmaceutical
30 composition comprising a therapeutically effective amount
of a compound of the invention and a pharmaceutically
acceptable carrier. In one embodiment, the amount of the
compound is an amount from about 0.01 mg to about 800 mg.
In another embodiment, the amount of the compound is an

amount from about 0.01 mg to about 500 mg. In another embodiment, the amount of the compound is an amount from about 0.01 mg to about 250 mg. In another embodiment, the amount of the compound is an amount from about 0.1 mg to about 60 mg. In another embodiment, the amount of the compound is an amount from about 1 mg to about 20 mg. In a further embodiment, the carrier is a liquid and the composition is a solution. In another embodiment, the carrier is a solid and the composition is a tablet. In a further embodiment, the carrier is a gel and the composition is a suppository.

This invention provides a pharmaceutical composition made by combining a therapeutically effective amount of a compound of this invention and a pharmaceutically acceptable carrier.

This invention provides a process for making a pharmaceutical composition comprising combining a therapeutically effective amount of a compound of this invention and a pharmaceutically acceptable carrier.

This invention provides a use of a compound of this invention for the preparation of a pharmaceutical composition for treating an abnormality, wherein the abnormality is alleviated by decreasing the activity of a human Y5 receptor. In different embodiments, the abnormality is an eating disorder, obesity, bulimia nervosa, a sexual disorder, a reproductive disorder, depression, an epileptic seizure, hypertension, cerebral hemorrhage, congestive heart failure, or a sleep disturbance.

In the subject invention a "therapeutically effective amount" is any amount of a compound which, when administered to a subject suffering from a disease against which the compounds are effective, causes reduction, remission, or regression of the disease.

In the practice of this invention the "pharmaceutically acceptable carrier" is any physiological carrier known to those of ordinary skill in the art useful in formulating pharmaceutical compositions.

In one preferred embodiment the pharmaceutical carrier may be a liquid and the pharmaceutical composition would be in the form of a solution. In another equally preferred embodiment, the pharmaceutically acceptable carrier is a solid and the composition is in the form of a powder or tablet. In a further embodiment, the pharmaceutical carrier is a gel and the composition is in the form of a suppository or cream. In a further embodiment the compound may be formulated as a part of a pharmaceutically acceptable transdermal patch.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example,

calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

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Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by for example, intramuscular, intrathecal, epidural, intraperitoneal or subcutaneous injection. Sterile solutions can also be

administered intravenously. The compounds may be prepared as a sterile solid composition which may be dissolved or suspended at the time of administration using sterile water, saline, or other appropriate sterile injectable medium. Carriers are intended to include necessary and inert binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings.

The compound can be administered orally in the form of a sterile solution or suspension containing other solutes or suspending agents (for example, enough saline or glucose to make the solution isotonic), bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like.

The compound can also be administered orally either in liquid or solid composition form. Compositions suitable for oral administration include solid forms, such as pills, capsules, granules, tablets, and powders, and liquid forms, such as solutions, syrups, elixirs, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions, and suspensions.

Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular compound in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular subject being treated will result in a need to adjust dosages, including subject age, weight, gender, diet, and time of administration.

One skilled in the art will readily appreciate that appropriate biological assays will be used to determine the therapeutic potential of the claimed compounds for treating the above noted disorders.

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This invention further provides compositions which need not be pharmaceutical as that term is understood in the art. Such compositions comprise a compound in accordance with the subject invention in an amount effective to
10 agonize and/or antagonize a Y5 receptor and a suitable carrier.

Still further, the invention provides a method of agonizing and/or antagonizing a Y5 receptor which
15 comprises contacting the receptor, e.g. in vitro or in vivo, with an amount of a compound of this invention effective to agonize and/or antagonize the receptor.

This invention will be better understood from the
20 Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow
thereafter.

Experimental Details and Results

I. Synthetic Methods for Examples

A. Triazine Compounds

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General Procedures relating to Examples:

For the stepwise addition of amines to cyanuric chloride (2,4,6-trichloro-1,3,5-triazine), see, for example, 10 Campbell, J.R. and Hatton, R.E., 1961; and Nestler, H. and Furst, H., 1963.

For more recent references concerning the formation of amino-1,3,5-triazines, see, for example, Kreutzberger, A, 15 et al., 1991; US 4383113; and US 3947374.

For the formation of cyanoguanidines from amines and sodium dicyanamide ($\text{NaN}(\text{CN})_2$) and/or formation of the biguinides, see, for example, Shaw, J. T. and Gross, F. 20 J., 1959; Curd, F. H. S., et al., 1948; Curd, F. H. S. and Rose, F. L., 1946; May, E. L., 1947; and Neelakantan, L., 1957.

The cyclization of biguinides to 2,4-diamino-1,3,5- 25 triazines can be accomplished using a number of carboxylic acid derivatives such as acid chlorides, esters, anhydrides, carboxylates, etc. See, for example, Furukawa, M., et al., 1961; Koshelev, V. N., et al., 1995; Tsitsa, P., et al., 1993; Shaw, J. T., et al., 1959; 30 Vanderhoek, R., et al., 1973; Nagasaka, H., et al., 1967; US 3891705; US 5348956; and US 5258513.

All reactions were performed under an inert atmosphere (Argon) and the reagents, neat or in appropriate solvents,

were transferred to the reaction vessel via syringe and cannula techniques. The parallel synthesis reaction arrays were performed in vials (without an inert atmosphere) using J-KEM heating shakers (Saint Louis, MO). Unless stated otherwise all solvents were AR grade and used as supplied. Anhydrous solvents were purchased from Aldrich Chemical Company and used as received. The examples described in the patent (1-58) were named using ACD/Name program (version 2.51, Advanced Chemistry Development Inc., Toronto, Ontario, M5H2L3, Canada).

Flash chromatography (silica gel, mesh size 230-400) and preparative thin layer chromatography (Analtech, 2000 micron) were used for chromatographic separations. Thin layer chromatography was used for analytical analysis of the mixtures. ^1H NMR spectra were recorded on a GE (QE Plus, 300 MHz) instrument and the spectra were either calibrated by the lock signal of the deuterated solvent or tetramethylsilane (TMS) as the internal standard. Signals in the ^1H NMR spectra are described as: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; sextet; septet; m, multiplet; b, broad. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, New Jersey.

General Procedure for the Synthesis of the Amino Side Chains ($\text{H}_2\text{N}-(\text{CH}_2)_n$ -pyrazole and imidazole):

The synthesis of 5-(1H-1-pyrazolyl)-1-pentanamine is typical: Sodium hydride (1.2 mol-equivalents) was added to a mixture of pyrazole or imidazole (one mol-equivalent) and 1-N-bromoalkylphthalimide (one mol-equivalent) in DMF (1 M with respect to the reagents). Once the bubbling subsided, the mixture was heated at reflux temperature for two days. The reaction mixture was cooled, triturated with

water, the precipitate was collected, washed with water and dried under reduced pressure to give the phthalimide protected product.

5 A mixture of the phthalimide such as 2-[5-(1H-1-pyrazolyl)pentyl]-1,3-isoindolinedione and hydrazine (one equivalent) in methanol were heated to reflux temperature for 12 hours and cooled. 1 N HCl (1-5 equivalents) was added and the mixture was filtered and washed with
10 methanol and water and then concentrated to give 5-(1H-1-pyrazolyl)-1-pentanamine as a viscous oil. (Scheme 1G)

General Procedure for the Synthesis of the Amino Side chains such as:

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N1-[4-(aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide

N1-[4-(aminomethyl)cyclohexyl]methyl-4-fluoro-1-benzenesulfonamide

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N1-[4-(aminomethyl)cyclohexyl]methyl-4-(tert-butyl)-1-benzenesulfonamide

N'-[4-(aminomethyl)cyclohexyl]methyl-N,N-dimethylsulfamide

25

Dimethylsulfamoyl chloride (one mol-equivalent, ClSO₂N(CH₃)₂) was added to a stirred solution of 1,4-bis-aminomethylcyclohexane (3 mol-equivalents) and diisopropylethylamine (1 mol-equivalent) in dichloromethane at 0°C. The reaction mixture was stirred at room temperature for 24 hours, concentrated under reduced
30 pressure and chromatographed (silica) to give the desired product as viscous oils. (Scheme 1A)

N1-[4-(aminomethyl)cyclohexyl]methyl-4-fluoro-1-benzenesulfonamide: Synthesized According to Scheme 1A, ¹H

NMR (CDCl₃) 7.86 (m, 2H), 7.19 (apparent t, J=8.1 Hz), 4.65 (broad, 1H), 2.86 and 2.78 (two d, 2H, ratio of 2:1 respectively, J=7.2 and 6.9 Hz respectively), 2.55 and 2.50 (two d, 2H, ratio of 2:1 respectively, J=6.3 Hz each), 1.82-0.90 (m, 10H).

General Procedure for the synthesis of 2,4-dichloro-6-amino-1,3,5-Triazines:

One mole equivalent of the amine was added dropwise to a solution of one mole-equivalent of 1,3,5-trichlorotriazine and 2 mole-equivalents of diisopropylethylamine in dichloromethane or THF at -78 °C under argon. The resulting solution was stirred for 1 hour at -78 °C, quenched with ether, precipitated salts removed by filtration, solvent removed under reduced pressure and the crude product was chromatographed (silica) to give the desired product.

2,4-Dichloro-6-isopropylamino-1,3,5-triazine:

Isopropylamine (neat, 4.13 g, 69.8 mmol) was added dropwise to a stirred solution of diisopropylethylamine (9.02 g, 69.8 mmol) and 2,4,6-trichlorotriazine (12.9 g, 69.8 mmol) in 100 ml of dry THF at -78 °C under argon. The resulting mixture was stirred at -78 °C for 0.5 hour, 200 ml of ether was added, filtered and the solids were washed with ether. The combined filtrates were concentrated and chromatographed (5% ethyl acetate-hexane, silica) to give 8.06 g of the desired product: Synthesized According to Scheme 2 and 3; ¹H NMR (CDCl₃) 5.80 (broad, 1H, 4.21 (septet, 1H, J=6.6 Hz), 1.25 (d, 6H, J=6.6 Hz)

2,4-Dichloro-6-cyclopropylamino-1,3,5-triazine:

Synthesized According to Scheme 2 and 3; ¹H NMR (CDCl₃)

5.93 (broad, 1H), 2.88 (m, 1H), 0.94 (m, 2H), 0.63 (m, 1H).

5 **General Procedure for the Synthesis of 2-Chloro-4,6-diamino-1,3,5-triazines:**

One mole-equivalent of an amine, one mol-equivalent of 2,4-dichloro-6-amino-1,3,5-triazines and 2 mole-equivalents of diisopropylethylamine were stirred at room
10 temperature for 3 days. The solvent was removed under reduced pressure and the crude product was chromatographed on silica to give the desired product:

15 N1-{[4-({[4-Chloro-6-(isopropylamino)-1,3,5-triazin-2-yl]amino)methyl]cyclohexyl)methyl}-1-naphthalenesulfonamide: A suspension of 2,4-dichloro-6-isopropyltriazine (1.04 g, 5.02 mmol), diisopropylethylamine (1.50 g, 10.0 mmol) and cyclohexylmethylaniline (1.66 g, 5.00 mmol) in 15 ml of dry
20 THF were stirred at room temperature for 3 days under argon. The initial suspension turned clear. The solvent was removed under reduced pressure, the solids were partitioned between ethyl acetate-hexane (50 ml, 1:9) and water (50 ml), separated and solvent removed to give 2.75
25 g of a white solid in 60% yield: Synthesized According to Scheme 2; 503 and 505 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.62 (d, 1H, J=8.7 Hz), 8.25 (d, 1H, J=8.7 Hz), 8.07 (d, 1H, J= 8.0 Hz), 7.95 (dd, J=8.0, 0.9 Hz), 7.72-7.50 (m, 3H), 5.20-3.95 (m, 4H), 4.04 (septet, 1H, J=6.6 Hz), 3.21 and 3.06
30 (two t, 2H, J=6.6 Hz), 2.72 (t, 2H, J=6.6 Hz), 1.80-0.65 (m, 7H), 1.19 (d, 6H, J=6.6 Hz).

General Procedure for the Synthesis of 2,4,6-Triamino-1,3,5-triazines from 2,4-diamino-6-chlorotriazines:

5

Parallel synthesis was used to prepare the triaminotriazines. The crude products were chromatographed (Preparative TLC) to give the final products.

10

A solution of 0.0200 mmol of N1-{[4-({[4-Chloro-6-(isopropylamino)-1,3,5-triazin-2-yl]amino}methyl)cyclohexyl]methyl}-1-naphthalenesulfonamide, 10 mg of a primary or secondary amine and 30 μ l of diisopropylethylamine in 200 μ l of DMF or dioxane were heated to 100-140 °C for at least 8 hours. The resulting mixture was cooled, applied to a preparative thin layer chromatography plate (2000 microns, Analtech) and eluted with an appropriate solvent to give the desired product. In cases where DMF was used as the solvent, a side product corresponding to a dimethylamino substitution (Example 17) of the chloro group of N1-{[4-({[4-chloro-6-(isopropylamino)-1,3,5-triazin-2-yl]amino}methyl)cyclohexyl]methyl}-1-naphthalenesulfonamide in about 20% yield was also obtained especially when primary amines were used to displace the chloro group. This product was separated from the desired product using Preparative Thin Layer Chromatography. (Scheme 2)

30

General Procedure for the Synthesis of 2,4,6-Triamino-1,3,5-triazines from 2,4-diamino-6-chlorotriazines:

A mixture of 2,4-diethylamino-6-chloro-1,3,5-triazine (1 mol-equivalents), diisopropylethylamine (one mol-equivalent) and 1,4-bis-aminomethylcyclohexane (3 equivalents) in dioxane were heated at reflux temperature for 3 days, cooled, concentrated and chromatographed on silica to give N1-[4-(aminomethyl)cyclohexyl]methyl-N3,N5-diethyl-1,3,5-benzenetriamine in 65% yield: Anal. Calc. for $C_{15}H_{29}N_7$: C, 58.60; H, 9.51; N, 31.89. Found: C, 58.84; H, 9.61; N, 31.64; 1H NMR ($CDCl_3$) 4.78 (broad, 3H), 3.45-3.10 (m, 6H), 2.60 and 2.51 (two d, 2H, $J=6.3$ Hz), 1.90-0.70 (m, 11H), 1.17 (t, 6H, $J=7.3$ Hz). (Scheme 3)

General Procedure for the Synthesis of 2,4,6-Triamino-1,3,5-triazines Containing Sulfonyl Ureas from 2,4-diamino-6-chlorotriazines or 2,4,6-Triaminotriazines Containing Dimethylamino Sulfonyl Ureas:

A transamination reaction was used to synthesize the sulfonyl ureas from dimethylaminosulfonyl ureas. A solution of one mol-equivalent of dimethyl sulfonyl urea, two mol-equivalents of diisopropylethylamine and one mol-equivalent of an amine such as morpholine or cyclopropylamine were heated at 100 °C in dioxane for 16 hours. The reaction mixture was cooled, concentrated and chromatographed to give the desired product. (Schemes 4A, 4B, 4C, and 4D)

Compounds in Table 1 (DMF as solvent unless otherwise noted):

Example 1

Synthesized According to Scheme 2.

N1-{[4-({[4-(Isopropylamino)-6-(methylamino)-1,3,5-
5 triazin-2-yl]amino}methyl)cyclohexyl]methyl}-1-
naphthalenesulfonamide: 60% yield (90% yield in dioxane),
Anal. Calc. For $C_{25}H_{35}N_7O_2S_1+0.2H_2O$: C, 59.90; H, 7.12; N, 19.56. Found: C, 59.91; H, 7.31; N, 19.23; 498 (MH^+ , ESI);
10 1H NMR ($CDCl_3$) 8.63 (d, 1H, $J=8.5$ Hz), 8.24 (dd, 1H, $J=7.2$, 0.9 Hz), 8.07 (d, 1H, $J=8.4$ Hz), 7.95 (dd, 1H, $J=7.2$, 0.9 Hz), 7.68-7.52 (m, 3H), 4.73 (broad, 4H), 4.11 (m, 1H), 3.13 (m, 2H), 2.88 (broad, 3H), 2.72 (apparent t, 2H, $J=6.6$ Hz), 1.90-0.70 (m, 7H), 1.16 (d, 6H, $J=6.3$ Hz).

15

Example 2

Synthesized According to Scheme 2.

N1-[4-([4-(ethylamino)-6-(isopropylamino)-1,3,5-triazin-2-
20 yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide:
41% yield, 512 (MH^+ , ESI); 1H NMR ($CDCl_3$) 8.64 (d, 1H, $J=8.7$ Hz), 8.25 (dd, 1H, $J=8.7$, 1.3 Hz), 8.08 (d, 1H, $J=8.0$ Hz), 7.96 (dd, 1H, $J=8.0$, 1.3 Hz), 7.70-7.50 (m, 3H), 4.76 (broad, 1H), 4.10 (broad, 1H), 3.37 (broad, 1H),
25 3.14 (broad, 1H), 2.73 (apparent t, 2H, $J=6.6$ Hz), 1.80-0.65 (m, 9H), 1.18 (d, 6H, $J=6.6$ Hz), 1.15 (t, 2 H, $J=7.2$ Hz).

Example 3

30

Synthesized According to Scheme 2.

N1-{[4-({[4-(Allylamino)-6-(isopropylamino)-1,3,5-triazin-
2-yl]amino}methyl)cyclohexyl]methyl}-1-
naphthalenesulfonamide: 20% yield (84% yield in dioxane);

Anal. Calc. for $C_{27}H_{37}N_7O_2S_1 + 1.0H_2O$: C, 59.87; N, 7.26; N, 18.10. Found: C, 60.32; H, 7.08; N, 17.89; 524 (MH^+ , ESI); 1H NMR ($CDCl_3$) 8.62 (d, 1H, $J=8.6$ Hz), 8.24 (dd, 1H, $J=8.6$, 1.3 Hz), 8.07 (d, 1H, $J=8.1$ Hz), 7.95 (dd, 1H, $J=8.1$, 0.6 Hz), 7.68-7.52 (m, 3H), 5.90 (ddt, 1H, $J=17.1$, 10.3, 1.5 Hz), 5.20 (apparent dq, 1H, $J=17.1$, 1.5 Hz), 5.10 (apparent dq, 1H, $J=10.3$, 1.5 Hz), 4.85 (broad, 1H), 4.62 (m, 1H), 4.08 (broad, 1H), 3.97 (m, 2H), 3.14 (m, 2H), 2.72 (t, 2H, $J=6.6$ Hz), 1.80-0.70 (m, 11H), 1.16 (d, 6H, $J=6.6$ Hz).

Example 4

Synthesized According to Scheme 2.

N1-{[4-([4,6-Di(isopropylamino)-1,3,5-triazin-2-yl]amino)methyl]cyclohexylmethyl}-1-naphthalenesulfonamide: 29% yield; 526 (MH^+ , ESI); 1H NMR ($CDCl_3$) 8.64 (d, 1H, $J=8.4$ Hz), 8.24 (d, 1H, $J=7.5$ Hz), 8.07 (d, 1H, $J=8.4$ Hz), 7.95 (dd, 1H, $J=7.5$ Hz), 7.68-7.52 (m, 3H), 5.10-4.40 (broad, 3H), 4.71 (apparent t, 1H, $J=6.6$ Hz), 4.15 (m, 2H), 3.18 (m, 2H), 2.72 (apparent t, 2H, $J=6.6$ Hz), 2.20-0.65 (m, 7H), 1.17 (d, 12H, $J=6.6$ Hz).

Example 5

Synthesized According to Scheme 2.

N1-[4-([4-(isopropylamino)-6-(propylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexylmethyl]-1-naphthalenesulfonamide: 55% yield; 526 (MH^+ , ESI); 1H NMR ($CDCl_3$) 8.65 (d, 1H, $J=8.7$ Hz), 8.25 (d, 1H, $J=8.0$ Hz), 8.08 (d, 1H, $J=8.0$ Hz), 7.95 (d, 1H, $J=8.0$ Hz), 7.72-7.50 (m, 3H), 5.10 (broad, 1H), 4.88 (m, 1H), 4.09 (m, 1H), 3.40-3.00 (m, 4H), 2.72 (apparent t, 2H, $J=6.6$ Hz), 1.80-

0.65 (m, 9H), 1.18 (d, 6H, J=6.6 Hz), 0.94 (t, 3H, J=7.2 Hz).

5

Example 6

Synthesized According to Scheme 2.

10 M1-[4-([4-(butylamino)-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide: 56% yield; 540 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.65 (d, 1H, J=8.7 Hz), 8.25 (d, 1H, J=8.0 Hz), 8.08 (d, 1H, J=8.0 Hz), 7.95 (d, 1H, J=8.0 Hz), 7.70-7.50 (m, 3H), 5.20-4.60
15 (broad, 3H), 4.10 (broad, 1H), 3.33 (broad, 2H), 3.14 (broad, 2H), 2.72 (apparent t, 2H, J=6.6 Hz), 1.70-0.60 (m, 11H), 2.72 (d, 6H, J=6.6 Hz), 0.92 (t, 3H, J=7.1 Hz).

Example 7

20

Synthesized According to Scheme 2.

M1-[4-([4-(cyclobutylamino)-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide: 58% yield; 538 (MH⁺, ESI); ¹H NMR
25 (CDCl₃) 8.65 (d, 1H, J=8.7 Hz), 8.25 (dd, 1H, J=8.7, 0.9 Hz), 8.08 (d, 1H, J=8.0 Hz), 7.95 (dd, 1H, J=8.0, 0.9 Hz), 7.72-7.52 (m, 3H), 5.50-4.50 (broad, 4H), 4.40 (m, 1H), 4.09 (M, 1H), 3.13 (m, 2H), 2.72 (apparent t, 2H, J=6.6 Hz), 2.34 (m, 2H), 2.00-0.65 (m, 13H), 1.17 (d, 6H, J=6.6
30 Hz).

Example 8

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Synthesized According to Scheme 2.

N1-[4-([4-(cyclopropylamino)-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-

10 naphthalenesulfonamide: 57% yield; 524 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.67 (d, 1H, J=8.7 Hz), 8.26 (d, 1H, J=7.5 Hz), 8.09 (d, 1H, J=8.1 Hz), 7.70-7.52 (m, 3H), 5.20-4.60 (broad, 4H), 4.11 (broad, 1H), 3.14 (broad, 2H, 2.71 2.19 (broad, 2H), 1.80-0.40 (m, 11H), 1.16 (d, 6H, J=6.3 Hz).

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Example 9

Synthesized According to Scheme 2.

N1-[4-([4-(isopropylamino)-6-(pentylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-

20 naphthalenesulfonamide: 49% yield; 554 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.64 (d, 1H, J=8.7 Hz), 8.24 (dd, 1H, J=8.7, 1.3 Hz), 8.08 (d, 1H, J= 8.0 Hz), 7.95 (d, J=8.0 Hz), 7.72-7.50 (m, 3H), 5.05 (broad, 1H), 4.78 (broad, 1H), 3.81 (broad, 2H), 3.14 (broad, 1H), 2.72 (apparent t, 2H, J=6.6 Hz), 1.80-0.65 (m, 13H), 1.18 (d, 6H, J=6.6 Hz), 0.89 (t, 3H, J=7.1 Hz).

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Example 10

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Synthesized According to Scheme 2.

N1-[4-([4-[(2-cyanoethyl)amino]-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-

naphthalenesulfonamide: 43% yield; 537 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.64 (d, 1H, J=8.7 Hz), 8.24 (dd, 1H, J=8.7, 1.3

Hz), 8.08 (d, 1H, J= 8.0 Hz), 7.95 (d, J=8.0 Hz), 7.72-7.50 (m, 3H), 6.08 (broad, 1H), 5.30 (broad, 1H), 4.81 (apparent t, 1H, J=6.6 Hz), 4.08 (broad, 1H), 3.70-2.50 (m, 6H), 1.80-0.65 (m, 7H), 1.17 (d, 6H, J=6.6 Hz).

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Example 11

Synthesized According to Scheme 2.

10 N1-[4-([4-[(2-hydroxyethyl)amino]-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide: 36% yield; 528 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.64 (d, 1H, J=8.7 Hz), 8.24 (d, 1H, J=8.7 Hz), 8.07 (d, 1H, J= 8.0 Hz), 7.95 (d, J=8.0 Hz), 7.72-7.50 (m, 3H), 5.58 (broad, 1H), 5.26 (broad, 1H), 5.10 (broad, 1H), 15 4.91 (broad, 1H), 4.08 (broad, 1H), 3.70 (t, 2H, J=6.6 Hz), 3.37 (p, 2H, J=6.6 Hz), 3.203.50-2.65 (m, 4H), 1.80-0.65 (m, 7H), 1.18 (d, 6H, J=6.6 Hz).

Example 12

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Synthesized According to Scheme 2.

N1-(4-[(4-(isopropylamino)-6-[(2-methoxyethyl)amino]-1,3,5-triazin-2-ylamino)methyl]cyclohexylmethyl)-1-naphthalenesulfonamide: 63% yield; 542 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.64 (d, 1H, J=8.7 Hz), 8.24 (dd, 1H, J=8.7, 1.3 Hz), 8.08 (d, 1H, J= 8.0 Hz), 7.95 (d, J=8.0 Hz), 7.72-7.50 (m, 3H), 5.93 (broad, 1H), 5.23 (broad, 1H), 4.80 (apparent t, 1H, J=6.6 Hz), 4.10 (m, 1H), 3.60-3.05 (m, 6H), 3.75 (s, 3H), 2.72 (t, apparent t, 2H, J=6.6 Hz), 30 1.75-0.65 (m, 7H), 1.17 (d, 6H, J=6.6 Hz).

Example 13

Synthesized According to Scheme 2.

N1-(4-[(4-(isopropylamino)-6-[(3-methoxypropyl)amino]-1,3,5-triazin-2-ylamino)methyl]cyclohexylmethyl)-1-naphthalenesulfonamide: 83% yield; 556 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.64 (d, 1H, J=8.7 Hz), 8.24 (dm, 1H, J=8.7 Hz), 8.07 (d, 1H, J= 8.0 Hz), 7.95 (d, J=8.0 Hz), 7.72-7.50 (m, 3H), 6.30-5.80 (broad, 2H), 5.20-4.50 (broad, 2H), 4.10 (broad, 1H), 3.60-3.05 (m, 6H), 2.72 (apparent t, 2H, J=6.6 Hz), 1.80-0.65 (m, 9H), 1.18 (d, 6H, J=6.6 Hz).

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Example 14

Synthesized According to Scheme 2.

N1-{[4-({[4-{[2-(dimethylamino)ethyl]amino}-6-(isopropylamino)-1,3,5-triazin-2-yl]amino}methyl)cyclohexyl]methyl}-1-naphthalenesulfonamide: 78% yield; 555 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.63 (d, 1H, J=8.5 Hz), 8.24 (dd, 1H, J=7.2, 0.9 Hz), 8.07 (d, 1H, J=8.4 Hz), 7.95 (dd, 1H, J=7.2, 0.9 Hz), 7.68-7.52 (m, 3H), 5.70-4.60 (broad, 3H), 4.15 (septet, 1H, J=6.6 Hz), 3.70 (broad, 1H), 3.45 (m, 2H), 3.14 (m, 2H), 2.71 (apparent t, 2H, J=6.3 Hz), 2.53 (t, 2H, J= 6.0 Hz), 2.30 (s, 6H), 1.80-0.65 (m, 7H), 1.17 (d, 6H, J= 6.6 Hz).

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Example 15

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Synthesized According to Scheme 2.

N1-[4-([4-[3-(1H-1-imidazolyl)propyl]amino-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide: 93% yield; 592 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.69 (d, 1H, J=8.7 Hz), 8.26 (d, 1H, J=7.5 Hz), 8.09 (d, 1H, J=8.1 Hz), 7.70-7.52 (m, 4H), 7.05 (m, 1H), 6.94 (m, 1H), 6.15 (broad, 1H), 5.70-5.00 (broad, 3H), 4.02 (t, 2H, J=6.9 Hz), the triplet at 4.02 partially covers a multiplet at

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4.09 (1H), 3.40-3.00 (m, 4H), 2.71 (t, 2H, J=6.3 Hz),
2.00-0.65 (m, 13H), 1.16 (d, 6H, J=6.7 Hz).

Example 16

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Synthesized According to Scheme 2.

N1-({4-[(4-(isopropylamino)-6-[(4-methoxyphenethyl)amino]-1,3,5-triazin-2-yl)amino)methyl]cyclohexyl)methyl)-1-

10 naphthalenesulfonamide: 50% yield, 618 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.64 (d, 1 H, J=8.7 Hz), 8.24 (dd, 1H, J=7.5, 0.9 Hz), 8.09 (d, 1H, J=8.1 Hz), 7.95 (d, J=8.0 Hz), 7.70-7.52 (m, 3H), 5.10-4.60 (m, 4H), 4.15 (m, 1H), 3.79 (s, 3H), 3.54 (m, 2H), 3.14 (m, 2H), 2.80 (m, 2H), 2.71 (t, 2H, J=6.6 Hz), 1.80-0.65 (m, 7H), 1.17 (d, 6H).

Example 17

Synthesized According to Scheme 2.

20 N1-{[4-({[4-(dimethylamino)-6-(isopropylamino)-1,3,5-triazin-2-yl]amino}methyl)cyclohexyl]methyl}-1-naphthalenesulfonamide: 512 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.63 (d, 1H, J=8.7 Hz), 8.25 (dd, 1H, J= 8.7, 1.3 Hz), 8.08 (d, 1H, J=8.0 Hz), 7.95 (dd, 1H, J= 8.0, 1.3 Hz), 25 7.72-7.50 (m, 3H), 5.90 (broad, 1H), 4.65 (apparent t, 1H, J=6.6 Hz), 4.12 (septet, 1H, J=6.6 Hz), 3.15 (m, 2H), 3.09 (broad s, 6H), 2.72 (apparent t, 2H, J=6.6 Hz), 1.80-0.65 (m, 7H), 1.18 (d, 6H, J=6.6 Hz).

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Example 18

Synthesized According to Scheme 2.

N1-[4-([4-[ethyl(methyl)amino]-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-

naphthalenesulfonamide: 58% yield; 556 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.64 (d, 1 H, J=8.7 Hz), 8.24 (dd, 1H, J=7.5, 0.9 Hz), 8.09 (d, 1H, J=8.1 Hz), 7.95 (d, J=8.0 Hz), 7.70-7.52 (m, 3H), 4.68 (t, 1H, J=6.3 Hz), 4.12 (septet, 1H, J= 6.6 Hz), 3.57 (q, 2H, J=7.1 Hz), 3.13 (t, 2H, J=6.6 Hz), 3.03 (broad s, 3H), 2.72 (t, 2H, J=6.6 Hz), 1.80-0.65 (m, 7H), 1.18 (d, 6H, J=6.6 Hz), 1.12 (t, 3H, J=7.1 Hz).

Example 19

Synthesized According to Scheme 2.

N1-[4-([4-(diethylamino)-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-

naphthalenesulfonamide: 95% yield; 540 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.64 (d, 1H, J=8.7 Hz), 8.26 (d, 1H, J=8.7 Hz), 8.07 (d, 1H, J= 8.0 Hz), 7.96 (d, J=8.0 Hz), 7.72-7.50 (m, 3H), 5.50-4.50 (broad, 2H), 4.10 (septet, 1H, J=6.6 Hz), 3.52 (q, 4H, J=7.1 Hz), 3.13 (apparent t, 2H, J=6.6 Hz), 2.71 (apparent t, 2H, J=6.6 Hz), 1.80-0.65 (m, 7H), 1.17 (d, 6H, J=6.6 Hz), 1.14 (t, 6H, J=7.1 Hz).

Example 20

Synthesized According to Scheme 2.

N1-[4-([4-(isopropylamino)-6-tetrahydro-1H-1-pyrrolyl-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-

naphthalenesulfonamide: 12% yield; 538 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.64 (d, 1H, J=8.7 Hz), 8.25 (dd, 1H, J=8.7, 1.3 Hz), 8.07 (d, 1H, J= 8.0 Hz), 7.95 (d, J=8.0, Hz), 7.72-7.50 (m, 3H), 5.15 (broad, 1H), 4.90 (broad, 1H), 4.70 (broad, 1H), 4.12 (septet, 1H, J=6.6 Hz), 3.50 (m, 4H), 3.15 (apparent t, 2H, J=6.6 Hz), 2.72 (apparent t, 2H, J= 6.6 Hz), 1.70-0.60 (m, 11H), 1.18 (d, 6H, J=6.6 Hz).

Example 21

Synthesized According to Scheme 2.

N1-(4-[(4-(isopropylamino)-6-[(2S)-2-

(methoxymethyl)tetrahydro-1H-1-pyrrolyl]-1,3,5-triazin-2-ylamino)methyl]cyclohexylmethyl)-1-naphthalenesulfonamide: 87% yield; 554 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.64 (d, 1 H, J=8.7 Hz), 8.24 (dd, 1H, J=7.5, 0.9 Hz), 8.09 (d, 1H, J=8.1 Hz), 7.95 (d, J=8.0 Hz), 7.70-7.52 (m, 3H), 5.50-4.40 (m, 4H), 4.15 (m, 1H), 3.92 (m, 2H), 3.70-3.20 m, 6H), 3.75 (s, 3H), 2.72 (t, 2H, J=6.6 Hz), 2.20-0.60 (m, 11H), 1.17 (d, 6H).

Example 22

Synthesized According to Scheme 2.

N1-{[4-([4-(isopropylamino)-6-piperidino-1,3,5-triazin-2-yl]amino)methyl]cyclohexylmethyl}-1-

naphthalenesulfonamide: Anal. Calc. For

C₂₉H₄₁N₇O₂S₁+0.3EtOAc: C, 62.74; H, 7.57; N, 16.96. Found: C, 62.70; H, 7.57; N, 16.94; 552 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.64 (d, 1 H, J=8.7 Hz), 8.24 (dd, 1H, J=7.5, 0.9 Hz), 8.09 (d, 1H, J=8.1 Hz), 7.95 (d, J=8.0 Hz), 7.70-7.52 (m, 3H), 4.67 (b, 2H), 4.55 (b, 1H), 4.11 (septet, 1H, J=6.3 Hz), 3.67 (m, 4H), 3.48 (apparent t, 2 H, J=5.7 Hz), 3.30 (apparent t, 2 H, J= 5.7 Hz), 3.14 (m, 2H), 2.71 (t, 2H, J=6.3 Hz), 2.00-0.60 (m, 13H), 1.16 (d, 6H, J=6.3 Hz).

Example 23

Synthesized According to Scheme 2.

N1-[4-([4-(isopropylamino)-6-(2-methylpiperidino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexylmethyl]-1-

naphthalenesulfonamide: 92% yield; 566 (MH⁺, ESI); ¹H NMR

(CDCl₃) 8.64 (d, 1 H, J=8.7 Hz), 8.24 (dd, 1H, J=7.5, 0.9 Hz), 8.09 (d, 1H, J=8.1 Hz), 7.95 (d, J=8.0 Hz), 7.70-7.52 (m, 3H), 5.10-4.60 (broad, 4H), 4.15 (septet, 1H, J=6.6 Hz), 3.40-2.70 (m, 6H), 2.80 and 2.64 (two s, 3H), 2.74 (apparent t, 2H, J=6.3 Hz), 1.75-0.60 (m, 13H), 1.13 (d, 6H, J=6.6 Hz).

Example 24

10 Synthesized According to Scheme 2.

M1-[4-([4-(isopropylamino)-6-morpholino-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide: 93% yield; 554 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.64 (d, 1 H, J=8.7 Hz), 8.24 (dd, 1H, J=7.5, 0.9 Hz), 8.09 (d, 1H, J=8.1 Hz), 7.95 (d, J=8.0 Hz), 7.70-7.52 (m, 3H), 5.2-4.6 (broad, 4H), 4.15 (septet, 1H, J=6.6 Hz), 4.00-3.00 (m, 8H), 2.72 (t, 2H, J=6.6 Hz), 1.80-0.60 (m, 7H), 1.18 (d, 6H, J=6.6 Hz).

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Example 25

Synthesized According to Scheme 2.

N1-{[4-([4-[(2R,6S)-2,6-dimethyl-1,4-oxazinan-4-yl]-6-(isopropylamino)-1,3,5-triazin-2-yl]amino}methyl)cyclohexyl]methyl}-1-naphthalenesulfonamide: 94% yield, 582 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.63 (d, 1H, J=8.5 Hz), 8.24 (dd, 1H, J=7.2, 0.9 Hz), 8.07 (d, 1H, J=8.4 Hz), 7.95 (dd, 1H, J=7.2, 0.9 Hz), 7.68-7.52 (m, 3H), 4.76-4.30 (m, 4H), 4.09 (septet, 1H, J=6.6 Hz), 3.54 (m, 4H), 3.14 (apparent t, 2H, J=6.6 Hz), 2.74 (t, 2H, J=6.6 Hz), 2.60-0.65 (m, 7H), 1.18 (d, 6H, J=6.6 Hz), 1.16 (dm, 6H, J=6.6 Hz).

Example 26

Synthesized According to Scheme 2.

N1-[4-([4-[(2-hydroxyethyl)(methyl)amino]-6-

5 (isopropylamino)-1,3,5-triazin-2-

yl]aminomethyl)cyclohexyl]methyl-1-naphthalenesulfonamide:

93% yield; 542 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.64 (d, 1 H, J=8.7 Hz), 8.24 (dd, 1H, J=7.5, 0.9 Hz), 8.09 (d, 1H, J=8.1 Hz), 7.95 (d, J=8.0 Hz), 7.70-7.52 (m, 3H), 5.10-
10 4.60 (broad, 4H, 4.15 m, 1H), 3.75-2.80 (m, 6H), 3.05 (s, 3H), 2.72 (t, 2H, J=6.6 Hz), 1.80-0.65 (m, 7H), 1.18 (d, 6H, J= 6.6 Hz).

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Example 27

Synthesized According to Scheme 2.

N1-{[4-([4-(4-acetylpiperazino)-6-(isopropylamino)-1,3,5-
20 triazin-2-yl]amino)methyl)cyclohexyl]methyl}-1-

naphthalenesulfonamide: 77% yield; 595 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.63 (d, 1H, J=8.5 Hz), 8.24 (d, 1H, J=7.2 Hz), 8.07 (d, 1H, J=8.4 Hz), 7.95 (d, 1H, J=7.2 Hz), 7.68-7.52 (m, 3H), 5.00-4.40 (broad, 3H), 4.70 (t, 1H, J=6.6 Hz),
25 4.15 (septet, 1H, J=6.6 Hz), 3.71 (m, 4H), 3.61 (m, 2H), 3.47 (m, 2H), 3.15 (m, 2H), 2.72 (t, 2H, J=6.3 Hz), 2.13 (s, 3H), 1.90-0.65 (m, 7H), 1.17 (d, 6H, J= 6.6 Hz).

Example 28

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Synthesized According to Scheme 2.

N1-{[4-([4-(isopropylamino)-6-(4-isopropylpiperazino)-
1,3,5-triazin-2-yl]amino)methyl)cyclohexyl]methyl}-1-

naphthalenesulfonamide: 60% yield; 595 (MH⁺, ESI); ¹H NMR

(CDCl₃) 8.64 (d, 1H, J=8.5 Hz), 8.24 (dd, 1H, J=7.2, 0.9 Hz), 8.07 (d, 1H, J=8.4 Hz), 7.95 (dd, 1H, J=7.2, 0.9 Hz), 7.68-7.52 (m, 3H), 5.20-4.40 (broad, 2H), 4.71 (apparent t, 1H, J=6.6 Hz), 4.13 (septet, 1H, J=6.6 Hz), 3.76 (m, 4H), 3.16 (apparent t, 2H, J=6.6 Hz), 2.74 overlapping a multiplet (t, 3H, J=6.6 Hz), 2.53 (m, 4H), 1.64 (ABm, 4H), 1.50-0.60 (m, 3H), 1.16 (d, 6H, J=6.6 Hz), 1.06 (d, 6H, J=6.6 Hz).

Compounds in Table 2 (dichloromethane as solvent):

Example 29

Synthesized According to Scheme 3.

N1-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-

yl]aminomethyl)cyclohexyl)methyl-4-(tert-butyl)-1-

benzenesulfonamide: 40% yield; Anal. Calc. For C₂₅H₄₁N₇SO₂ + 0.10 CH₂Cl₂: C, 59.60; H, 8.20; N, 19.40. Found: C, 58.42; H, 7.98; N, 18.16; 504 (MH⁺, ESI); ¹H NMR (CDCl₃) 7.80 (d, 2H, J=8.6 Hz), 7.50 (d, 2H, J= 8.6 Hz), 5.40 (broad, 1H), 5.20-4.75 (broad, 3H), 3.40-3.15 (m, 6H), 2.75 (t, 2H, J=4.5 Hz), 1.80-1.10 (m, 14H), 1.25 (s, 9H), 0.80-0.70 (broad, 2H).

Example 30

Synthesized According to Scheme 3.

N1-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-

yl]aminomethyl)cyclohexyl)methyl-4-fluoro-1-

benzenesulfonamide: 30% yield, Anal. Calc. For C₂₁H₃₀N₇FSO₂ + 0.10 CH₂Cl₂: C, 54.10; H, 6.90; N, 21.00.

Found: C, 53.77; H, 6.75; N, 20.43; ^1H NMR (CDCl_3) 7.85 (d, 2H, $J=8.6$ Hz), 7.15 (d, 2H, $J=8.6$ Hz), 5.00-4.50 (broad, 4H), 3.40-3.15 (m, 6H), 2.80-2.70 (m, 2H), 1.80-1.20 (m, 14H), 0.90-0.80 (broad, 2H).

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Example 31

Synthesized According to Scheme 3.

10 N1-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-2-methoxy-5-methyl-1-benzenesulfonamide: 86% yield; 492 (MH^+ , ESI); Anal. Calc. for $\text{C}_{23}\text{H}_{37}\text{N}_7\text{O}_3\text{S}_1+1.5\text{CH}_3\text{OH}$: C, 54.52; H, 8.03; N, 18.17. Found: C, 54.09; H, 7.84; N, 18.18; ^1H NMR (CDCl_3) 7.81 (m, 1H), 7.33 (broad d, 1H, $J=8.0$ Hz), 6.93 (d, 1H, $J=8.0$ Hz), 5.20-4.60 (broad, 4H), 3.94 (s, 3H), 3.50-3.10 (m, 15 6H), 2.76 and 2.67 (two t, 2H, $J=6.3$ Hz), 2.50-2.30 (m, 4H), 1.90-0.70 (m, 11H), 1.17 (t, 6H, $J=7.2$ Hz).

Example 32

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Synthesized According to Scheme 3.

N1-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-2-fluoro-1-benzenesulfonamide: 86% yield; 466 (MH^+ , ESI); Anal. Calc. for $\text{C}_{21}\text{H}_{32}\text{F}_1\text{N}_7\text{O}_2\text{S}_1+1.5\text{CH}_3\text{OH}$: C, 52.61; H, 7.46; N, 19.09. Found: C, 52.14, H, 7.10; N, 19.17; ^1H NMR (CDCl_3) 7.90 (m, 1H), 7.58 (m, 1H), 7.40-7.18 (m, 2H), 5.50-4.60 (broad, 4H), 3.50-3.10 (m, 6H), 2.91 and 2.82 (two t, 2 H, $J=6.2$ Hz), 1.90-0.60 (m, 11H), 1.17 (t, 6H, $J=7.2$ Hz).

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Example 33

Synthesized According to Scheme 3.

N1-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-2-methyl-1-benzenesulfonamide: 28% yield; 462 (MH⁺, ESI); Anal. Calc. for C₂₂H₃₅N₇O₂S₁+0.7CH₃OH: C, 56.33; H, 7.87, N, 20.26. Found: C, 56.34; H, 7.82; N, 20.01; ¹H NMR (CDCl₃) 7.40 (m, 4H), 5.10-4.60 (broad, 4H), 4.26 and 4.25 (two t, 2H, J=6.2 Hz), 2.10-0.70 (m, 11H), 1.18 (t, 6H, J=7.2 Hz).

Example 34

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Synthesized According to Scheme 3.

N3-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-3-pyridinesulfonamide: 94% yield; 449 (MH⁺, ESI); Anal. Calc. for C₂₀H₃₂N₈O₂S₁+1.5CH₃OH: C, 52.00; H, 7.71; N, 22.56. Found: C, 51.84; H, 7.65; N, 22.27; ¹H NMR (CDCl₃) 9.08 (m, 1H), 8.81 (dm, 1H, J=5.3 Hz), 8.16 (dm, 1H, J=8.1 Hz), 7.46 (ddm, 1H, J=5.3, 8.1 Hz), 5.20-4.60 (broad, 4H), 3.50-3.10 (m, 6H), 2.92 and 2.83 (two d, 2H, J= 6.3 Hz), 1.85-0.80 (m, 11H), 1.15 (t, 6H, J=7.3 Hz).

20

Example 35

Synthesized According to Scheme 3.

N1-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-4-methoxy-1-benzenesulfonamide: 86% yield; 478 (MH⁺, ESI); Anal. Calc. for C₂₂H₃₅N₇O₃S₁+0.5CH₃OH: C, 54.30; H, 7.46; N, 20.15. Found: C, 54.30; H, 7.42; N, 19.66; ¹H NMR (CDCl₃) 7.80 (dm, 2H, J=8.9 Hz), 6.98 (dm, 2H, J= 8.9 Hz), 5.20-4.60 (broad, 4H), 3.86 (s, 3H), 1.90-0.70 (m, 11H), 1.16 (t, 6H, J=7.3 Hz).

30

Example 36

Synthesized According to Scheme 3.

5 N5- [4- ([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-2,4-dimethyl-1,3-oxazole-5-sulfonamide: 86% yield; 467 (MH⁺, ESI); Anal. Calc. for C₂₀H₃₄N₈O₃S₁: C, 51.48; H, 7.34; N, 24.01. Found: C, 51.26; H, 7.34; N, 23.81; ¹H NMR (CDCl₃) 5.10-4.50 (broad, 4H), 3.50-2.70 (m, 6H), 2.64 (two s, 3H), 2.40 (two s, 3H), 10 2.10-0.80 m, 11H), 1.18 t, 6H, J=7.3 Hz).

Example 37

Synthesized According to Scheme 3.

15 N2- [4- ([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-2-thiophenesulfonamide: 93% yield; 454 (MH⁺, ESI); Anal. Calc. for C₁₉H₃₁N₇O₂S₂+0.5H₂O: C, 49.33; H, 6.97; N, 21.19. Found: C, 49.36; H, 6.91; N, 20.82; ¹H NMR (CDCl₃) 7.62 (m, 2H), 20 7.10 (m, 1H), 5.30-4.50 (broad, 3H), 3.50-2.80 (m, 8H), 2.60-1.90 (b, 1H), 1.90-0.70 (m, 11H), 1.17 (t, 6H, J=7.3 Hz).

Example 38

25

Synthesized According to Scheme 3.

N4- [4- ([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-methyl-1H-4-imidazolesulfonamide: 90% yield; 452 (MH⁺, ESI); Anal. 30 Calc. for C₁₉H₃₃N₉O₂S₁+0.7CH₃OH: C, 49.92; H, 7.61; N, 26.59. Found: C, 49.65; H, 7.18; N, 27.09; ¹H NMR (CDCl₃) 7.50 (m, 1H), 7.46 (m, 1H), 5.50-4.80 (broad, 4H), 3.75 (s, 3H), 3.50-2.70 (m, 6H), 2.70-2.00 (broad, 1H), 1.90-0.70 (m, 11H), 1.16 (t, 6H, J=6.3 Hz).

Example 39

Synthesized According to Scheme 3.

5 N1-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-4-methyl-1-benzenesulfonamide: 95% yield; 462 (MH⁺, ESI); Anal. Calc. for C₂₂H₃₅N₇O₂S₁+0.5CH₃OH: C, 56.58; H, 7.81; N, 20.53. Found: C, 56.79; H, 7.74; N, 20.36; ¹H NMR (CDCl₃) 7.76 (dm, 2H, J=8.1 Hz), 7.32 (dm, 2H, J=8.1 Hz), 5.30-4.6 (broad, 4H), 3.50-3.00 (m, 6H), 2.42 (s, 3H), 1.90-0.70 (m, 11H), 1.14 (t, 6H, J=7.3 Hz).

10

Example 40

15 Synthesized According to Scheme 3.

N5-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-2,1,3-benzothiadiazole-5-sulfonamide: 84% yield; 506 (MH⁺, ESI); ¹H NMR (CDCl₃) 8.27 (m, 2H), 7.73 (m, 1H), 5.60 (broad, 1H), 5.40 (broad, 3H), 3.45-3.00 (m, 6H), 2.82 and 2.72 (two d, 2H, J=6.8 Hz), 1.80-0.70 (m, 11H), 1.15 (t, 6H, 7.3 Hz).

20

Example 41

25 Synthesized According to Scheme 3.

N8-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-8-quinolinesulfonamide: 48% yield; 499 (MH⁺, ESI); Anal. Calc. for C₂₄H₃₄N₈O₂S₁+0.5CH₃OH: C, 57.18; H, 7.05; N, 21.77. Found: C, 57.22; H, 7.15; N, 21.67; ¹H NMR (CDCl₃) 9.03 (m, 1H), 8.45 (dm, 1H, J=8.0 Hz), 8.30 (d, 1H, J=8.0 Hz), 8.06 (dm, 1H, J=8.0 Hz), 7.67 (mt, 1H, J=8.0 Hz), 7.57 (dd, 1H, 4.8, 8.0 Hz) 6.34 (m, 1H), 4.88 (broad, 3H), 3.50-3.00 (m, 6H),

30

2.76 and 2.67 (two t, 2H, J=6.4 Hz), 2.30 (broad, 2H, 1.80-0.70 (m, 11H), 1.15 (t, 6H, J=7.3 Hz).

Example 42

5

Synthesized According to Scheme 3.

N-[4-([4,6-di(ethylamino)-1,3,5-triazin-2-

yl]aminomethyl)cyclohexyl]methylmethanesulfonamide: 55%

yield; 386 (MH⁺, ESI); Anal. Calc. for C₁₆H₃₁N₇O₂S₁+0.5CH₃OH:

10 C, 49.35; H, 8.28; N, 24.42. Found: C, 49.10; H, 7.78; N, 24.81; ¹H NMR (CDCl₃) 5.20-4.60 (broad, 5H), 3.50-3.00 (m, 8H), 2.95 and 2.93 (two s, 3H), 1.90-0.70 (m, 11H), 1.18 (t, 6H).

15

Compounds in Table 3 (dioxane as solvent):

Example 43

Synthesized According to Scheme 4A.

20

N1-[4-([4-(isopropylamino)-6-tetrahydro-1H-1-pyrrolyl-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-

pyrrolidinesulfonamide: 35% yield; Anal. Calc. For

C₂₂H₄₀N₈SO₂ + 0.10 CH₂Cl₂: C, 54.26; H, 8.28; N, 22.91.

Found: C, 53.93; H, 8.25; N, 22.86; 481 (MH⁺, ESI); ¹H NMR

25

(CDCl₃) 5.00-4.80 (m, 1H), 4.80-4.60 (m, 1H), 4.60-4.40 (m, 1H), 3.60-3.40 (m, 6H), 2.95-2.80 (m, 3H), 1.90-1.80 (m, 8H), 1.50-1.30 (m, 8H), 1.20-1.050 (m, 6H), 0.90-0.80 (m, 2H).

30

Example 44

Synthesized According to Scheme 4B.

N4-[4-([4-(isopropylamino)-6-morpholino-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-4-morpholinesulfonamide:

30% yield; Anal. Calc. For $C_{22}H_{40}N_8SO_2 + 1.10 CH_2Cl_2$: C, 48.30; H, 7.40; N, 19.60. Found: C, 48.16; H, 7.28; N, 20.01; 513 (MH⁺, ESI); ¹H NMR (CDCl₃) 5.05-4.60 (m, 3H), 3.80-3.60 (m, 12H), 3.35-3.10 (m, 6H), 3.05-2.80 (m, 3H), 1.80-1.30 (m, 8H), 1.20-1.05 (m, 6H), 1.00-0.80 (m, 2H).

Example 45

Synthesized According to Scheme 4B.

10 N1-[4-([4-(isopropylamino)-6-piperidino-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-1-piperidinesulfonamide: 30% yield; Anal. Calc. For $C_{24}H_{44}N_8SO_2 + 0.3 CH_2Cl_2$: C, 54.64; H, 8.41; N, 20.98. Found: C, 54.53; H, 8.24; N, 20.94; 509 (MH⁺, ESI); ¹H NMR (CDCl₃) 4.80-4.60 (m, 1H), 4.60-4.50 (m, 1H), 4.20-4.10 (m, 1H), 3.80-3.60 (m, 4H), 3.40-3.30 (m, 2H), 3.20-3.10 (m, 4H), 3.00-2.90 (m, 3H), 1.80-1.40 (m, 20H), 1.20-1.050 (m, 6H), 0.90-0.80 (m, 2H).

Example 46

20

Synthesized According to Scheme 2.

N1-[(4-[(4,6-ditetrahydro-1H-1-pyrrolyl-1,3,5-triazin-2-yl)amino]methylcyclohexyl)methyl]-4-(tert-butyl)-1-benzenesulfonamide: 30% yield; Anal. Calc. For $C_{29}H_{45}N_7SO_2 + 0.2 CH_2Cl_2$: C, 61.20; H, 8.00; N, 17.10. Found: C, 61.60; H, 8.12; N, 16.41; 556 (MH⁺, ESI); ¹H NMR (CDCl₃) 7.75 (d, 2H, J=8.7 Hz), 7.50 (d, 2H, J=8.7 Hz), 4.85 (broad, 1H), 4.70-650 (broad, 1H), 3.60-3.50 (broad, 8H), 3.20 (t, 2H, J=7.5 Hz), 2.75 (t, 2H, J=7.5 Hz), 1.95-1.15 (m, 16H), 1.15 (s, 9H), 0.90-0.80 (m, 2H).

30

Example 47

Synthesized According to Scheme 4C and 4D.

N-cyclopropyl-*N'*-[4-([4-(cyclopropylamino)-6-(isopropylamino)-1,3,5-triazin-2-

yl]aminomethyl)cyclohexyl]methylsulfamide: 20% yield;

Anal. Calc. For $C_{20}H_{36}N_8SO_2 + 0.15 CH_2Cl_2$: C, 52.00; H, 7.86; N, 24.08. Found: C, 51.87; H, 7.83; N, 23.74; 453 (MH⁺, ESI); ¹H NMR (CDCl₃) 5.40-5.00 (m, 3H), 4.95-4.60 (m, 2H), 3.30-3.20 (m, 2H), 2.90-2.60 (m, 3H), 2.50-2.40 (m, 2H), 1.80-1.30 (m, 8H), 1.25-1.10 (m, 6H), 0.90-0.80 (m, 2H), 0.70-0.60 (m, 4H), 0.50-0.40 (m, 4H).

Example 48

Synthesized According to Scheme 2.

N'-[4-([4-(cyclopropylamino)-6-(isopropylamino)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl]methyl-*N,N*-

dimethylsulfamide: 28% yield; Anal. Calc. For $C_{19}H_{36}N_8SO_2 + 0.60 CH_3COOC_2H_5 + 0.10 CH_2Cl_2$: C, 50.90; H, 7.95; N, 22.30. Found: C, 50.42; H, 7.52; N, 22.87; 441 (MH⁺, ESI); ¹H NMR (CDCl₃) 4.90-4.80 (m, 1H), 4.70-4.60 (m, 1H), 4.50-4.40 (m, 1H), 4.20-4.10 (m, 1H), 3.40-3.20 (m, 3H), 3.10 (s, 6H), 3.00-2.80 (m, 3H), 1.90-1.30 (m, 8H), 1.15-1.05 (m, 6H), 0.95-0.85 (m, 2H), 0.70-0.50 (m, 4H).

Example 49

Synthesized According to Scheme 2.

*N*1-{[4-([4-chloro-6-(isopropylamino)-1,3,5-triazin-2-yl]amino)methyl)cyclohexyl]methyl}-1-

naphthalenesulfonamide: 60% yield; 503.08 and 505.09 (MH⁺, ESI): 60% yield; ¹H NMR (CDCl₃) 8.62 (d, 1H, J=8.7 Hz), 8.25 (d, 1H, J=8.7 Hz), 8.07 (d, 1H, J=8.0 Hz), 7.95 (dd, J=8.0, 0.9 Hz), 7.72-7.50 (m, 3H), 5.20-3.95 (m, 4H), 4.04 (septet, 1H, J=6.6 Hz), 3.21 and 3.06 (two t, 2H, J=6.6

Hz), 2.72 (t, 2H, J=6.6 Hz), 1.80-0.65 (m, 7H), 1.19 (d, 6H, J=6.6 Hz).

Example 50

5

Synthesized According to Scheme 3.

N'-[(4-[(4,6-dimorpholino-1,3,5-triazin-2-

yl)amino]methylcyclohexyl)methyl]-*N,N*-dimethylsulfamide:

40% yield; Anal. Calc. For $C_{21}H_{38}N_8SO_2$ + 0.70 CH_2Cl_2 : C, 46,80; H, 6.75; N, 19.90. Found: C, 46.68; H, 6.75; N, 19.98; 1H NMR ($CDCl_3$) 4.90-4.80 (m, 1H), 4.60-4.50 (m, 1H), 3.80-3.60 (m, 16H), 3.20 (t, 2H, J=4.5 Hz), 2.75 (t, 2H, J=4.5 Hz), 2.8 (s, 6H), 1.8-1.3 (m, 8H), 1.1-0.9 (m, 2H).

15

Example 51

Synthesized According to Scheme 2.

*N*l-[4-([4-chloro-6-(isopropylamino)-1,3,5-triazin-2-

yl]aminomethyl)cyclohexyl)methyl-4-(*tert*-butyl)-1-

benzenesulfonamide: 30% yield; 509 (MH^+ , ESI); 1H NMR ($CDCl_3$) 7.80 (d, 2H, J=8.80 Hz), 7.50 (d, 2H, J=8.80 Hz), 5.30-5.20 (m, 1H), 4.70-4.50 (m, 2H), 3.35-3.25 (m, 2H), 2.90-2.75 (m, 3H), 1.80-1.30 (m, 8H), 1.35 (s, 9H), 1.25-1.15 (m, 6H), 0.90-0.85 (m, 2H).

25

Example 52

Synthesized According to Scheme 2.

*N*l-[4-([4-(cyclopropylamino)-6-tetrahydro-1*H*-1-pyrrolyl-

1,3,5-triazin-2-yl]aminomethyl)cyclohexyl)methyl-4-fluoro-

1-benzenesulfonamide: 504 (MH^+ , ESI); 1H NMR ($CDCl_3$) 7.65 (d, 2H, J=8.7 Hz), 6.63 (d, 2H, J=8.7 Hz), 4.95-4.70 (m, 2H), 4.30 (m, 1H), 3.50 (m, 3H), 3.40-3.20 (m, 4H), 2.85

30

(t, 2H, J=5.5 Hz), 1.90 (m, 4H), 1.80-1.30 (m, 8H), 0.90 (m, 2H), 0.70 (m, 2H), 0.50 (m, 2H)

Example 53

5

Synthesized According to Scheme 2.

N'-((4-(((4,6-dichloro-1,3,5-triazin-2-yl)amino)methyl)cyclohexyl)methyl)-N,N-dimethylsulfamide:

35% yield; 397 (MH⁺, ESI); ¹H NMR (CDCl₃) 6.40 (m, 1H),
10 4.65-4.55 (m, 1H), 3.40 (t, 2H, J=5.20 Hz), 3.0 (t, 2H, J=5.20 Hz), 2.80 (s, 6H), 1.85-1.30 (m, 8H), 0.950-0.85 (m, 2H).

Example 54

15

Synthesized According to Scheme 2.

N1-[(4-[(4,6-ditetrahydro-1H-1-pyrrolyl-1,3,5-triazin-2-yl)amino]methylcyclohexyl)methyl]-2-methoxy-5-methyl-1-

benzenesulfonamide: 35% yield; Anal. Calc. For
20 C₂₇H₄₁N₇SO₃+0.35 CH₂Cl₂: C, 57.30; H, 7.35; N, 17.10. Found: C, 57.72; H, 7.43; N, 16.43; ¹H NMR (CDCl₃) 7.7 (s, 1H), 7.40-7.30 (dd, 1H), 6.90 (d, 1H), 4.90-4.80 (m, 2H), 3.95 (s, 3H), 3.60-3.40 (broad s, 8H), 3.25 (t, 2H, J=5.5 Hz), 2.75 (t, 2H, J=5.5), 2.30 (s, 3H), 1.95-1.85 (broad, s,
25 8H), 1.80-1.20 (m, 8H), 0.95-0.8 (m, 2H).

Example 55

Synthesized According to Scheme 5.

30 N1-[4-([4-(cyclopropylamino)-6-(2-pyridyl)-1,3,5-triazin-2-yl]aminomethyl)cyclohexyl)methyl-4-fluoro-1-benzenesulfonamide

N1-[4-(aminomethyl)cyclohexyl]methyl-4-fluoro-1-benzenesulfonamide: A solution of 2.37 g of 4-fluorophenylsulfonyl chloride (12.2 mmol) in 30 ml of dichloromethane was added over 10 minutes to a stirred
5 solution of 5.20 g of 1,4-bis-aminomethylcyclohexane (36.6 mmol) and 3.15 g of diisopropylethylamine (24.4 mmol) in 100 ml of dichloromethane at room temperature. The reaction mixture was stirred at room temperature for 16 hours, concentrated, and chromatographed on 200 g of
10 silica packed with 5% MeOH (containing 2M NH_3)- CHCl_3 , eluted with 5%, 7.5%, 10% (1 liter each) to give 3.63 g of the desired product.

A mixture of 564 mg
15 N1-[4-(aminomethyl)cyclohexyl]methyl-4-fluoro-1-benzenesulfonamide (2.0 mmol) in MeOH was triturated with 1M HCl in ether. The precipitate was filtered and heated with 248 mg of cyclopropylcyanoguanidine (2.00 mmol) in 5 ml of 1-butanol for 16 hours. The solvent was removed in
20 vacuo and the product was used in the next step.

Piconinyl chloride (67.7 mg, 0.38 mmol) was added to a stirred mixture of 175 mg of biguanide (0.38 mmol) in acetone-5%aqueous NaOH (3 mL, 2:1) at 0 °C (ice bath).
25 After five minutes, the ice bath was removed and the mixture was stirred for 1 hour at room temperature. The solvent was removed and chromatographed on silica to give the desired compound: 11% yield; 512 (MH^+ , ESI); ^1H NMR (CDCl_3) 8.75 (m, 1H), 7.90-7.70 (m, 7H), 7.20 (m, 1H),
30 7.10 (m, 1H), 5.60 (broad, 1H), 5.40 (broad, 2H), 4.50 (broad, 1H), 3.45 (m, 2H), 3.00-2.60 (m, 4H), 1.90-1.00 (m, 11H), 1.00-0.50 (m, 4H).

Compounds in Table 4 (dioxan as solvent):

Example 56

5 Synthesized According to Scheme 2.

*N*2,*N*4-diethyl-*N*6-[5-(1*H*-1-pyrazolyl)pentyl]-1,3,5-triazine-2,4,6-triamine: ¹H NMR (CDCl₃) 7.54 (d, 1H, J=1.8 Hz), 7.32 (d, 1H, J=2.1 Hz), 6.19 (dd, 1H, J=1.8, 2.1 Hz), 5.10 (b, 3H), 4.08 (t, 2H, J=6.9 Hz), 3.32 (m, 6H), 1.85
10 (p, 2H, J=6.9 Hz), 1.54 (p, 2H, J=6.9 Hz), 1.31 (p, 2H, J=6.9 Hz), 1.12 (t, 6H, J=7.2 Hz).

Example 57

15 Synthesized According to Scheme 2.

*N*2,*N*4-diethyl-*N*6-[3-(1*H*-1-imidazolyl)propyl]-1,3,5-triazine-2,4,6-triamine: ¹H NMR (CDCl₃) 7.45 (s, 1H), 6.99 (s, 1H), 6.86 (s, 1H), 5.42 (broad, 1H), 5.15 (broad, 2H), 3.92 (t, 2H, J=6.9 Hz), 3.55 (broad, 1H), 3.31 (m, 6H),
20 1.98 (p, 2H, J=6.9 Hz), 1.10 (t, 6H, J=7.2 Hz).

Example 58

Synthesized According to Scheme 2.

25 *N*2,*N*4-diethyl-*N*6-(2-pyridylmethyl)-1,3,5-triazine-2,4,6-triamine: ¹H NMR (CDCl₃) 8.44 (d, 1H, J=4.8 Hz), 7.55 (apparent dt, 1H, J= 7.8, 1.3 Hz), 7.32 (d, 1H, J=7.8 Hz), 7.07 (dd, 1H, J=1.3, 4.8 Hz), 6.00 (broad, 1H), 4.63 (m, 2H), 3.32 (m, 4H), 1.08 (t, 6H, J=7.2 Hz).

I. Synthetic Methods for ExamplesB. Bicyclic Compounds5 **General Procedures relating to Examples:**

For the formation of 2-aminothiazoles from 2-haloketones and thioureas, see, for example, Kearney, P.C., et al., 1998; Di Fabio, R. and Pentassuglia, G., 1998; De Kimpe, N., et al., 1996; Plazzi, P.V., et al., 1995; and
10 Novikova, A. P., 1991.

For the formation of thiazoles from 2-haloketones and thioamides, see, for example, Critcher, D. J. and Pattenden, G., 1996; and Friedman, B. S., et al., 1937.

15

For the formation of 2-aminoimidazoles from 2-haloketones and guanidines, see, for example, Little, T. L. and Webber, 1994; and Chabaka, L.M., et al., 1994.

20

For the formation of imidazoles from 2-haloketones and amidines, see, for example, Demchenko, A. M., et al., 1997; and Nagao, Y., et al., 1996.

25

For the synthesis of 2-aminooxazoles from 2-haloketones and ureas, see, for example, Pathak, V.N., et al., 1993; Crangk, G. and Foulis, M.J., 1971; and Marchetti, E., et al., 1968.

30

For the formation of oxazoles from 2-haloketones and amides, see, for example, Hammar, W.J. and Rustad, M.A., 1981; and Zhao, Z., et al., 1991.

Benzotriazole-1-carboxaldehyde was purchased from Aldrich Chemical Company and is recommended for the formation of formamides from amines.

5 All reactions were performed under an inert atmosphere (Argon) and the reagents, neat or in appropriate solvents, were transferred to the reaction vessel via syringe and cannula techniques. Anhydrous solvents were purchased from Aldrich Chemical Company and used as received. The
10 examples 1-44 described in this application were named using ACD/Name program (version 2.51, Advanced Chemistry Development Inc., Toronto, Ontario, M5H2L3, Canada).

¹H and ¹³C spectra were recorded at 300 and 75 MHz (QE Plus) with CDCl₃ as solvent (unless otherwise noted) and tetramethylsilane as internal standard. s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; sextet; septet; b = broad; m = multiplet. Elemental analyses were performed by Robertson Microlit Laboratories, Inc. Low-
15 resolution electrospray MS spectra were measured (ESMS, MS) and MH⁺ is reported. Thin-layer chromatography (TLC) was carried out on glass plates precoated with silica gel 60 F₂₅₄ (0.25 mm, EM Separations Tech.). Preparative thin-
20 layer chromatography was carried out on glass sheets precoated with silica gel GF (2 mm, Analtech). Flash column chromatography was performed on Merck silica gel 60 (230 - 400 mesh). Melting points were determined in open capillary tubes on a Med-Temp apparatus and are
25 uncorrected.

General Procedure for the Synthesis of Bromoketones:

In general, to the solution of a ketone (1 equivalent) in acetic acid or an appropriate solvent, cooled in a water bath, was added bromine or a brominating agent such as tetrabutylammonium perbromide (1 equivalent) slowly. The reaction mixture was stirred at room temperature. The solvents were evaporated, the residue was dissolved in dichloromethane, and washed with saturated sodium bicarbonate and water. The organic phase was dried over sodium sulfate. Evaporation of the combined decolorized organic phase afforded a light yellow oil. In some cases, the desired product precipitated upon concentration of the reaction mixture.

General Procedure for the Synthesis of Bromoketones (from acetylpyridines).

To the solution of an acetylpyridine (1 equivalent) and concentrated hydrogen bromide (2 equivalents, 48% in acetic acid) and methanol (AcOH/MeOH = 3.5/1), was added bromine (1 equivalent) dropwise at room temperature with stirring. The reaction mixture was heated to 60 °C for 4 hours. The evaporation of the solvent afforded a yellow solid which was collected by filtration and washed with diethyl ether. The bromoketone was used for the next reaction without further purification.

2-Bromo-1-(2-pyridinyl)-1-ethanone hydrogen bromide was obtained as a yellow solid in 100% from 2-acetylpyridine and hydrogen bromide: ^1H NMR (CD_3OD) δ 8.81 (d, 1H, J = 5.4 Hz), 8.73 (t, 1H, J = 8.1 Hz), 8.27 (d, 1H, J = 8.1 Hz), 8.14 (t, 1H, J = 6.6 Hz), 3.92 (d, 1H, J = 11.4 Hz), 3.83 (d, 1H, J = 11.4 Hz).

2-Bromo-1-(3-pyridinyl)-1-ethanone hydrogen bromide was obtained as a yellow solid in more than 95% from 3-acetylpyridine and hydrogen bromide: ^1H NMR (CD_3OD) δ 8.96 (t, 1H, $J = 0.9$ Hz), 8.89 (d, 1H, $J = 6.0$ Hz), 8.88 (dt, 1H, $J = 1.5, 8.1$ Hz), 8.16 (dd, 1H, $J = 6.0, 8.0$ Hz), 3.82 (d, 1H, $J = 11.1$ Hz), 3.72 (d, 1H, $J = 11.1$ Hz).

2-Bromo-1-(4-pyridinyl)-1-ethanone hydrogen bromide was obtained as a yellow solid in more than 95% yield from 4-acetylpyridine and hydrogen bromide: ^1H NMR (CD_3OD) δ 8.90 (d, 2H, $J = 6.9$ Hz), 8.24 (d, 2H, $J = 6.9$ Hz), 3.79 (d, 1H, $J = 11.1$ Hz), 3.69 (d, 1H, $J = 11.1$ Hz).

2-Bromo-1-(2,5-dimethyl-1,3-thiazol-4-yl)-1-ethanone hydrogen bromide was obtained from 4-acyl-2,5-dimethyl-1,3-thiazole and bromine in acetic acid: 70% yield; ^1H NMR ($\text{DMSO}-d_6$) δ 5.48 (s, 1H), 3.37 (ABq, 2H), 2.91 (s, 3H), 2.54 (s, 3H).

2-Chloro-1-(thiophen-2-yl)-1-ethanone: Trimethylsilyl diazomethane (TMSCHN_2 , 2M in hexanes, 100 ml, 0.200 mole) was added dropwise, over a period of 20 minutes, to an ice bath solution of thiophene-2-acetyl chloride (0.192 mole, 28.1 g) in 100 ml of dry 1,4-dioxane. The slush disappeared upon addition of TMSCHN_2 . The reaction mixture was slowly warmed to room temperature and stirred for 24 hours. The reaction mixture was cooled in an ice bath and HCl gas was bubbled for 0.5 hour and stirred at room temperature for 2 days. The solvent was removed under reduced pressure, the residue partitioned between 100 ml of aqueous saturated NaHCO_3 solution and 250 ml of ethyl acetate and separated. The organic phase was washed with 100 ml of aqueous saturated NaHCO_3 solution, dried (Na_2SO_4)

and the solvent was removed under reduced pressure. The crude product was chromatographed on 200 g of silica packed with 2.5% EtOAc-hexanes and the column was eluted with increasing amounts of ethyl acetate in hexanes (2.5%,
5 1 L, 5%, 1 L; 7.5%, 1 L, 10%, 1 L; 12.5%, 1 L; 15%, 1 L) to give 12.8 g of the desired product which was slightly contaminated: 42% yield; ^1H NMR (CDCl_3) δ 7.80 (dd, 1H, $J=0.9$, 3.9 Hz), 7.74 (dd, 1H, $J=0.9$, 5.0 Hz average), 7.19 (dd, 1H, $J=0.9$, 5.0 Hz average), 4.61 (s, 2H). This
10 product turned yellow and then brown over time and therefore was used in the formation of the 2-amino-1,3-thiazole derivatives as soon as possible.

2-Bromo-1-(1,3-thiazol-2-yl)-1-ethanone hydrogen bromide:
15 tetra-n-Butylammonium perbromide (Bu_4NBr_3 , 17.3 g, 35.8 mmol) was added, over a period of 30 seconds, to a stirred solution of 2-acyl-1,3-thiazole (4.55 g, 35.8 mmol) in 100 ml of dichloromethane at room temperature. The resulting orange to red solution was stirred at room temperature for
20 48 hours and approximately half of the solvent was removed under reduced pressure, filtered and the solids were washed with 50% EtOAc/hexanes to afford 8.60 g (84%) of the desired product: ^1H NMR ($\text{DMSO}-d_6$) δ 8.92-8.60 (broad, 2H), 8.28 (d, 1H, $J=3.2$ Hz average), 8.17 (d, 1H, $J=3.2$
25 Hz average), 4.91 (s, 2H).

General Procedure for the Synthesis of Thioureas:

A protected diamine such as N-Boc-1,4-diaminobutane or N-Boc-1,5-diaminopentane (1 equivalent) was dissolved in
30 tetrahydrofuran and stirred at room temperature. Benzoyl isothiocyanate (1 equivalent) was added dropwise to the reaction mixture. The resulting mixture was stirred at room temperature for 24 hours and the solvent was removed

under reduced pressure to give a yellow oil. The yellow oil (1 equivalent) was then dissolved in methanol, and aqueous potassium carbonate (3 equivalents) solution added, and the mixture stirred for 48 hours. Water was added to the reaction mixture which was then extracted in 2x75 ml ethyl acetate. The combined extracts were washed with water, dried with anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to give the desired thiourea.

tert-Butyl 5-[(aminocarbothioyl)amino]pentylcarbamate was obtained as a light yellow wax from *tert*-butyl 5-[[[(benzoylamino)carbothioyl]amino]-pentylcarbamate: ^1H NMR (CD_3OD) δ 3.44 (m, 1H), 3.10 (m, 1H), 3.01 (t, 2H, $J = 6.7$ Hz), 1.60-1.31 (m, 6H), 1.41 (s, 9H); 262 (ESMS, MH^+).

tert-Butyl 5-[[[(benzoylamino)carbothioyl]amino]-pentylcarbamate was obtained a light yellow solid in 79% yield from *N*-BOC-1,5-diaminopentane and benzoyl isothiocyanate: m.p. 90-93 °C; ^1H NMR δ NMR data.

trans-tert-Butyl-{4-[(aminocarbothioyl)amino]cyclohexyl}-methylcarbamate was obtained as a light yellow wax from *trans-tert*-butyl-(4-[[[(benzoylamino)carbothioyl]amino]-cyclohexyl)-methylcarbamate: ^1H NMR (CD_3OD) δ 3.92 (m, 1H), 2.86 (m, 2H), 2.00 (m, 2H), 1.76 (m, 2H), 1.41 (s, 9H), 1.37 (m, 1H), 1.06 (m, 4H); 288 (ESMS, MH^+).

trans-tert-Butyl-(4-[[[(benzoylamino)carbothioyl]amino]-cyclohexyl)-methylcarbamate was obtained as a yellow solid in 97% yield from *tert*-butyl 4-aminocyclohexylmethylcarbamate and benzoyl isothiocyanate.

trans-*tert*-Butyl 4-aminocyclohexylmethylcarbamate was obtained in more than 95 % yield by hydrogenation of benzyl 4-{[(*tert*-butoxycarbonyl)amino]methyl} cyclocarbamate.

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Benzyl-4-[[[*tert*-butoxycarbonyl]amino]methyl] cyclohexylcarbamate: To a stirred suspension of 4-[[(*tert*-butoxycarbonyl)amino]methyl] cyclohexanecarboxylic acid (Maybridge Chemical Co., Ltd.) (45g) and diphenylphosphoryl azide (44 ml) in toluene (600 ml) was added triethylamine (32 ml) over a period of 20 min whilst maintaining the internal temperature at -10-0 C. The mixture was slowly warmed and then stirred at 70 C for 4h. After cooling to 40 C, benzyl alcohol (36 ml) was added and the reaction mixture heated at reflux for 20 h. The cold reaction mixture was washed with water and brine and dried over anhydrous magnesium sulfate. Removal of the solvent and recrystallization of the organic residue from ethyl acetate and diethyl ether gave the title compound, benzyl-4-[[[*tert*-butoxycarbonyl]amino]methyl]cyclohexylcarbamate as a white solid, m.p. 129-131 C.

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trans-Benzyl-4-{[(aminocarbothioyl)amino]methyl}-cyclohexylcarbamate was obtained as a yellow solid in 71% yield from *trans*-benzyl 4-({[(Benzoylamino)carbothioyl]-amino}methyl)-cyclohexylcarbamate; 322 (ESMS, MH⁺).

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trans-Benzyl 4-({[(benzoylamino)carbothioyl]amino}methyl)-cyclohexylcarbamate was obtained as a yellow solid from benzyl 4-(aminomethyl)cyclohexylcarbamate and benzoyl isothiocyanate.

trans-Benzyl 4-(aminomethyl)cyclohexylcarbamate was obtained as a white solid in more than 95% yield by stirring benzyl 4-{[(tert-butoxycarbonyl)amino]methyl}-cyclocarbamate in 2N HCl (made from 1 : 1 of EtOAc and 4N HCl in dioxane).

General Procedure for the Synthesis of Bicyclic Thiazoles:

A mixture of a bromoketone (1 equivalent), thiourea (1 equivalent), and diisopropylethylamine (2 equivalents) in acetone or anhydrous ethanol was heated at reflux overnight. The solvent was evaporated, the brown residue dissolved in dichloromethane and washed with saturated aqueous sodium bicarbonate solution. The mixture was extracted with dichloromethane three times. The combined extracts were dried over anhydrous sodium sulfate and the solvent removed to afford a crude product which was purified by flash column chromatography (silica gel, hexanes : ethyl acetate).

tert-Butyl-5-{[4-(2-pyridinyl)-1,3-thiazol-2-yl]amino}-pentyl-carbamate was obtained as a brown syrup in 97% yield from 2-bromo-1-(2-pyridinyl)-1-ethanone hydrogen bromide and tert-butyl 5-[(aminocarbothioyl)amino]pentylcarbamate: ^1H NMR δ 9.57 (m, 1H), 7.91 (d, 1H, J = 7.8 Hz), 7.70 (td, 1H, J = 1.5, 7.8 Hz), 7.27 (s, 1H), 7.16 (dd, 1H, J = 4.8, 7.2 Hz), 5.36 (b, 1H), 4.57 (b, 1H), 3.30 (q, 2H, J = 6.1 Hz), 3.12 (m, 2H), 1.68 (m, 2H), 1.56-1.42 (m, 4H), 1.44 (s, 9H).

tert-Butyl-5-{[4-(3-pyridinyl)-1,3-thiazol-2-yl]amino}-pentylcarbamate was obtained as a light yellow solid in 55% yield from 2-bromo-1-(3-pyridinyl)-1-ethanone hydrogen bromide and tert-butyl 5-[(aminocarbothioyl)amino]-

pentylcarbamate: ^1H NMR δ 9.03 (d, 1H, J = 1.8 Hz), 8.51 (dd, 1H, J = 0.9, 4.8 Hz), 8.07 (m, 1H), 7.29 (dd, 1H, J = 4.8, 7.8 Hz), 6.78 (s, 1H), 5.32 (m, 1H), 4.55 (b, 1H), 3.32 (q, 2H, J = 6.0 Hz), 3.15 (m, 2H), 1.74 (m, 2H), 1.48 (m, 4H), 1.45 (s, 9H); ESMS m/e = 362.95 (MH^+).

tert-Butyl-5-{[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino}-pentylcarbamate was obtained as a yellow solid in 51% yield from 2-bromo-1-(4-pyridinyl)-1-ethanone hydrogen bromide and tert-butyl 5-[(aminocarbothioyl)amino]pentylcarbamate: ^1H NMR δ 8.59 (dd, 2H, J = 1.5, 4.8 Hz), 7.65 (dd, J = 1.5, 4.8 Hz), 6.93 (s, 1H), 5.30 (b, 1H), 4.56 (b, 1H), 6.32 (q, 2H, J = 6.0 Hz), 3.14 (m, 2H), 1.75 (m, 2H), 1.48 (m, 2H), 1.44 (s, 9H); ESMS m/e = 362.87 (MH^+).

trans-Benzyl-4-({[4-(2-pyridinyl)-1,3-thiazol-2-yl]amino}-methyl)cyclohexylcarbamate was obtained as a dark brown oil from 2-bromo-1-(2-pyridinyl)-1-ethanone hydrogen bromide and trans-benzyl 4-[(aminocarbothioyl)amino]methyl}-cyclohexylcarbamate: ^1H NMR δ 8.57 (m, 1H), 7.89 (d, 1H, J = 7.2 Hz), 7.71 (m, 1H), 7.45 (m, 1H), 7.35 (m, 5H), 7.17 (m, 1H), 5.33 (m, 1H), 5.08 (s, 2H), 4.61 (m, 1H), 3.48 (m, 1H), 3.16 (t, 2H, J = 6.3 Hz), 2.07 (m, 2H), 1.88 (m, 2H), 1.63 (m, 1H), 1.13 (m, 4H); ESIMS m/e = 423.2 (MH^+).

trans-Benzyl-4-({[4-(3-pyridinyl)-1,3-thiazol-2-yl]amino}-methyl)cyclohexylcarbamate was obtained as a dark brown oil from 2-bromo-1-(3-pyridinyl)-1-ethanone hydrogen bromide and trans-benzyl 4-[(aminocarbothioyl)amino]methyl}-cyclohexylcarbamate: ^1H NMR δ 9.13 (d, 1H, J = 2.1 Hz), 8.83 (dd, 1H, J = 1.8, 4.8 Hz), 8.21 (m, 1H), 7.45 (m, 1H), 6.77 (s, 1H), 5.41 (m,

1H), 5.08 (s, 2H), 4.62 (m, 1H), 3.47 (m, 1H), 3.17 (t, 2H, $J = 6.5$ Hz), 2.07 (m, 2H), 1.89 (m, 2H), 1.61 (m, 1H), 1.13 (m, 4H); ESIMS $m/e = 423.2$ (MH^+).

5 *trans*-Benzyl-4-([4-(4-pyridinyl)-1,3-thiazol-2-yl]amino)-methyl)cyclohexylcarbamate was obtained as a dark brown oil from 2-bromo-1-(4-pyridinyl)-1-ethanone hydrogen bromide and *trans*-benzyl 4-{[(aminocarbothioyl)amino]methyl}-cyclohexylcarbamate: ¹H
10 NMR δ 8.59 (d, 2H, $J = 4.5$ Hz), 7.64 (d, 2H, $J = 4.5$ Hz), 6.93 (s, 1H), 5.31 (m, 1H), 5.08 (s, 2H), 4.60 (m, 1H), 3.49 (m, 1H), 3.18 (t, 2H, $J = 6.6$ Hz), 2.09 (m, 2H), 1.91 (m, 2H), 1.65 (m, 1H), 1.14 (m, 4H); ESIMS $m/e = 423.2$ (MH^+).

15 *tert*-Butyl N-{[4-([4-[1-(Phenylsulfonyl)-1H-3-pyrrolyl]-1,3-thiazol-2-yl]amino)cyclohexyl]methyl}carbamate: 73% yield, 517 (ESMS, MH^+); ¹H NMR ($CDCl_3$) δ 7.93 (d, 2H, $J=7.6$ Hz), 7.68-7.46 (m, 4H), 7.19 (m, 1H), 6.68 (b, 1H), 6.58
20 (m, 1H), 6.53 (s, 1H), 3.40 (m, 1H), 3.29 (m, 2H), 2.89 (t, 2H, $J=6.5$ Hz), 1.96 (ABm, 4H), 1.42 (s, 9H), 1.30-0.99 (m, 4H).

tert-Butyl N-[(4-[4-(1,3-thiazol-2-yl)-1,3-thiazol-2-yl]aminocyclohexyl)methyl]carbamate: 57% yield, 395 (ESMS, MH^+); ¹H NMR ($CDCl_3$) δ 7.79 (d, 1H, $J=3.4$ Hz), 7.28 (d, 1H, $J=3.1$ Hz), 7.19 (s, 1H), 5.12 (d, 1H, $J=8.0$ Hz), 4.61 (b, 1H), 3.26 (m, 1H), 3.01 (t, 2H, $J=6.5$ Hz), 2.05 (ABm, 4H), 1.44 (s, 9H), 1.30-1.02 (m, 5H).

30 *tert*-Butyl N-[(4-[4-(1,3-Thiazol-2-yl)-1,3-thiazol-2-yl]aminocyclohexyl)methyl]carbamate: 31% yield, 394 (ESMS, MH^+); ¹H NMR ($CDCl_3$) δ 7.74 (dd, 1H, $J=1.3, 8.3$ Hz), 7.51-7.39 (m, 2H), 5.91 (apparent d, 1H, $J=7.1$ Hz), 4.62 (b,

1H), 3.93 (m, 1H), 3.00 (apparent t, 2H, J=6.2 Hz), 1.98 (ABm, 4H), 1.77 (b, 1H), 1.44 (s, 9H), 1.43 (m, 1H), 1.28-1.09 (m, 4H).

5 *trans*-*tert*-Butyl N-[(4-[4-(5-phenyl-3-isoxazolyl)-1,3-thiazol-2-yl]aminocyclohexyl)methyl]carbamate: 75% yield, 455 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 7.89 (m, 2H), 7.44 (m, 3H), 7.09 (s, 1H), 6.83 (s, 1H), 5.62 (b, 1H), 4.61 (m, 1H), 3.31 (m, 1H), 3.03 (m, 2H), 2.08 (ABm, 4H), 1.47 (s, 10 9H), 1.42-1.05 (m, 5H).

trans-*tert*-Butyl N-[(4-[4-(2,5-dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminocyclohexyl)methyl]carbamate: 37% yield, 423 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 6.43 (s, 1H), 5.04 15 (d, 1H, J=8.2 Hz), 4.59 (m, 1H), 3.26 (m, 1H), 3.01 (d, 2H, J=6.0 Hz), 2.64 (s, 3H), 2.55 (s, 3H), 2.04 (ABm, 4H), 1.44 (s, 9H), 1.28-1.03 (m, 5H).

20 **General Procedure for the Deprotection of the Boc-bicyclic Thiazoles Intermediates:**

The Boc protected 2-amino-1,3-thiazole intermediate was treated with 2N hydrogen chloride in 1,4-dioxane and ethyl acetate (prepared from 4N HCl in dioxane) at room 25 temperature for 2 hours or longer as needed. The solvent was removed in vacuo and the desired compound was collected by filtration.

30 *trans*-N2-[4-(Aminomethyl)cyclohexyl]-4-(1,3-thiazol-2-yl)-1,3-thiazol-2-amine hydrochloride: 100% yield, 295 (ESMS, MH⁺); ¹H NMR (CD₃OD) δ 8.02 (d, 1H, J=3.6 Hz), 7.84 (d, 1H, J=3.6 Hz), 7.59 (s, 1H), 3.60 (m, 1H), 2.83 (d, 2H, J=7.0 Hz), 2.19 (ABm, 4H), 1.69 (m, 1H), 1.45 (m, 2H), 1.22 (m, 2H).

trans-N2-[4-(Aminomethyl)cyclohexyl]-4-(2,5-dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-amine hydrochloride: 100% yield, 323 (ESMS, MH⁺); ¹H NMR (CD₃OD) δ 7.02 (s, 1H), 3.72 (m, 1H), 2.88 (s, 3H), 2.81 (d, 2H, J=7.5 Hz), 2.56 (s, 3H), 2.06 (ABm, 4H), 1.68 (m, 1H), 1.46-1.14 (m, 4H).

trans-N2-[4-(Aminomethyl)cyclohexyl]-4-(5-phenyl-3-isoxazolyl)-1,3-thiazol-2-amine hydrochloride: 100% yield, 355 (ESMS, MH⁺); ¹H NMR (CD₃OD) δ 7.87 (m, 2H), 7.50-7.40 (m, 5H), 3.81 (m, 1H), 2.84 (d, 2H, J=7.5 Hz), 2.08 (ABm, 4H), 1.68 (m, 1H), 1.47-1.17 (m, 4H).

trans-N2-[4-(Aminomethyl)cyclohexyl]-4-[1-(phenylsulfonyl)-1H-3-pyrrolyl]-1,3-thiazol-2-amine hydrochloride: 100% yield, 417 (ESMS, MH⁺); ¹H NMR (CD₃OD) δ 8.00 (d, 2H, J=7.0 Hz), 7.88 (s, 1H), 7.71 (m, 1H), 7.60 (m, 2H), 7.36 (m, 1H), 6.90 (s, 1H), 6.67 (m, 1H), 3.65 (m, 1H), 2.83 (d, 2H, J=7.5 Hz), 2.06 (ABm, 4H), 1.69 (m, 1H), 1.54-1.13 (m, 4H).

N¹-[4-(2-Pyridinyl)-1,3-thiazol-2-yl]-1,5-pentanediamine trihydrogen chloride was obtained as a yellow solid in more than 95% yield from *tert*-butyl 5-{[4-(2-pyridinyl)-1,3-thiazol-2-yl]amino}pentylcarbamate: ¹H NMR (CD₃OD) δ 8.65 (d, 1H, J = 6.0 Hz), 8.48-8.37 (m, 2H), 7.85 (s, 1H), 7.80 (m, 1H), 3.51 (t, 2H, J = 6.6 Hz), 2.94 (m, 2H), 1.74 (m, 4H), 1.53 (m, 2H); ESIMS m/e = (MH⁺).

N¹-[4-(3-Pyridinyl)-1,3-thiazol-2-yl]-1,5-pentanediamine trihydrogen chloride was obtained as a yellow solid in more than 95% yield from *tert*-butyl 5-{[4-(3-pyridinyl)-1,3-thiazol-2-yl]amino}pentylcarbamate: ¹H NMR (CD₃OD) δ

9.29 (d, 1H, $J = 1.8$ Hz), 8.97 (m, 1H), 8.81 (d, 1H, $J = 5.7$ Hz), 8.14 (dd, 1H, $J = 5.7, 8.1$ Hz), 7.50 (s, 1H), 3.51 (t, 2H, $J = 6.9$ Hz), 2.94 (m, 2H), 1.75 (m, 4H), 1.55 (m, 2H); ESIMS $m/e = 262.85$ (MH^+).

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N^1 -[4-(4-Pyridinyl)-1,3-thiazol-2-yl]-1,5-pentanediamine trihydrogen chloride was obtained as a yellow solid in more than 95% yield from tert-butyl 5-{[4-(4-pyridinyl)-1,3-thiazol-2-yl]amino}pentylcarbamate: 1H NMR (CD_3OD) δ 8.79 (d, 2H, $J = 6.6$ Hz), 8.42 (d, 2H, $J = 6.6$ Hz), 7.90 (s, 1H), 3.50 (t, 2H, $J = 6.8$ Hz), 2.94 (m, 2H), 1.75 (m, 4H), 1.54 (m, 2H), ESIMS $m/e = 262.80$ (MH^+).

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$N1$ -[4-(5-Phenyl-3-isoxazolyl)-1,3-thiazol-2-yl]-1,5-pentanediamine hydrochloride: 50% yield from the corresponding commercial bromoketone: 1H NMR ($CDCl_3$) δ 7.90-7.79 (m, 2H), 7.55-7.45 (m, 3H), 7.22 (s, 1H), 7.10 (s, 1H), 3.42 (t, 2H, $J=5.6$ Hz), 3.30-3.22 (m, 2H), 2.95 (t, 2H, $J=5.6$ Hz), 1.80-1.42 (m, 6H)

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General Procedure for the Derivatization of Amines with Carboxylic Acid and Sulfonic Acid Derivatives:

An amine such as $N1$ -[4-(5-phenyl-3-isoxazolyl)-1,3-thiazol-2-yl]-1,5-pentanediamine (0.305 mmol) was dissolved in 2 ml CH_2Cl_2 containing 2 equivalents of diisopropylethylamine. A sulfonyl chloride, sulfamoyl chloride, acid chloride or carbamoyl chloride (1-3 equivalents) was added dropwise. The reaction mixture was stirred at room temperature for 1-3 days, quenched with water, washed with 10% $NaHCO_3$ solution, dried over Na_2SO_4 and chromatographed using column chromatography or preparative TLC.

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General Procedure for the Formation of Formamides:

tert-Butyl N-[4-
5 (isopropylamino)cyclohexyl]methylcarbamate:

Isopropyl iodide (2 equivalents) was added dropwise to a suspension of tert-butyl N-[4-aminocyclohexyl]methylcarbamate (1 equivalent) and diisopropylethyl amine (3
10 equivalents) in THF. The resulting mixture was stirred for 1 day. TLC analysis showed some starting amine. Additional isopropyl iodide (1 equivalent) and diisopropylethyl amine (3 equivalents) were added to the reaction mixture and heated at 40 °C for 1 day. The
15 reaction mixture was concentrated and chromatographed to give tert-butyl N-[4-(isopropylamino)cyclohexyl]methylcarbamate: 22% yield, 271 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 4.65 (broad, 1H), 2.91 (m, 3H), 2.42 (m, 1H), 1.80 (ABm, 4H), 1.38 (s, 9H), 0.98 (d, 6H, J=6.3 Hz), 1.32-0.85 (m, 5H).
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Similarly, tert-butyl N-[4-(2-methoxyethylamino)-cyclohexyl]methylcarbamate was obtained (2-methoxyethyl bromide and n-Bu₄NI were used): 35% yield, 378 (ESMS, MH⁺);
25 ¹H NMR (CDCl₃) δ 4.64 (broad, 1H), 3.44 (m, 2H), 3.31 & 3.30 (two s, 3H), 2.92 (m, 2H), 2.74 (m, 2H), 2.33 (m, 1H), 1.81 (ABm, 4H), 1.39 & 1.38 (two s, 9H), 1.34 (m, 1H), 0.98 (m, 4H).

30 tert-Butyl-N-[4-(isopropylformylamino)cyclohexyl]methylcarbamate:

A solution of a tert-butyl N-[4-(isopropylamino)-cyclohexyl]methylcarbamate (7.89 mmol, 1 equivalent) in 5 ml of THF was added dropwise to a solution of 1H-

benzotriazole-1-carboxaldehyde (8.68 mmol, 1.2 equivalents) in 10 ml of THF at room temperature. The reaction mixture was stirred overnight and heated at reflux temperature for two hours. 1H-benzotriazole-1-carboxaldehyde (additional 1 equivalent) was added to the reaction mixture and stirred overnight. The solvent was removed and dichloromethane was added to the residue. The organic phase was washed with 2N NaOH solution, saturated with NaCl solution, dried over Na₂SO₄, the solvent removed, and the residue chromatographed to give *tert*-butyl N-[4-(isopropylformylamino)cyclohexyl]-methyl-carbamate: 100% yield, 299 (ESMS, MH⁺); ¹H NMR (CD₃OD) δ 8.22 & 8.18 (two s, 1H), 4.63 (broad, 1H), 4.30 & 3.60 (two m, 1H), 3.76 (m, 1H), 2.99 (m, 2H), 1.44 (s, 9H), 1.27 (d, 3H, J=6.5 Hz), 1.21 (d, 3H, J=6.5 Hz), 1.91-0.82 (m, 9H).

Similarly, N-[4-(2-methoxyethylformylamino)cyclohexyl]-methylcarbamate was prepared: 58% yield; 315 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.25 & 8.16 (two s, 1H), 4.80 (broad, 1H), 4.07 & 3.23 (two m, 1H), 3.50 (m, 2H), 3.40-3.33 (m, 2H), 3.31 (s, 3H), 2.99 (m, 2H), 1.46 (s, 9H), 1.86-0.95 (m, 9H).

N-[4-(Aminomethyl)cyclohexyl]-N-isopropylformamide: Dioxane containing HCl was added (10 ml of 4N HCl solution) to a solution of *tert*-butyl N-[4-(isopropylformylamino)-cyclohexyl]methylcarbamate dissolved in 10 ml Et₂O, stirred at room temperature for 2 hours and the solvent removed under reduced pressure to obtain N-[4-(aminomethyl)cyclohexyl]-N-isopropylformamide: 100% yield, 199 (ESMS, MH⁺); ¹H NMR (CD₃OD) δ 8.16 (s, 1H), 4.16 & 3.57 (two m, 1H), 3.70 (m, 1H), 2.79 (m, 2H), 1.36 (m, 6H), 1.91-1.06 (m, 9H).

Similarly, *N*-[4-(aminomethyl)cyclohexyl]-*N*-(2-methoxyethyl)-formamide was obtained: 100% yield; 215 (ESMS, MH^+); 1H NMR (CD_3OD) δ 8.44 & 8.03 4.65 (two s, 1H), 3.79-3.36 (m, 7H), 3.71 (s, 3H), 2.12-1.13 (m, 9H).

N-Benzoyl-*N'*-[4-(isopropylformylamino)cyclohexyl]-methylthiourea:

A mixture of *N*-[4-(aminomethyl)cyclohexyl]-*N*-isopropyl-formamide salt (4.55 mmol, 1 equivalent), benzoyl isothiocyanate (5.46 mmol, 1.2 equivalent) and triethylamine (5.46 mmol, 1.2 equivalent) in THF (50 ml) were stirred at room temperature overnight. The removal of the solvent and chromatography (silica) afforded the desired product: 39% yield, 362 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 10.87 (broad, 1H), 9.20 (broad, 1H), 8.20 & 8.18 (two s, 1H), 7.83 (d, 2H, $J=7.7$ Hz), 7.60 (m, 1H), 7.49 (m, 2H), 4.26 (m, 1H), 3.76 & 3.08 (two m, 1H), 3.57 (m, 2H), 1.25 (d, 3H, $J=6.8$ Hz), 1.19 (d, 3H, $J=6.8$ Hz), 1.97-1.03 (m, 9H).

Similarly, *N*-Benzoyl-*N'*-[4-(2-methoxyethylformylamino)-cyclohexyl]methylthiourea was obtained: 100% yield, 378 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 10.85 (broad, 1H), 9.03 (broad, 1H), 8.18 & 8.08 (two s, 1H), 7.84 (d, 2H, $J=7.9$ Hz), 7.64 (m, 1H), 7.52 (d, 2H, $J=7.8$ Hz), 3.63-3.24 (m, 7H), 3.34 & 3.33 (two m, 3H), 2.03-1.13 (m, 9H).

N-[4-(Isopropylformylamino)cyclohexyl]methylthiourea:

An aqueous solution of K_2CO_3 (2 equivalents) in water was added to a solution of *N*-benzoyl-*N'*-[4-(isopropylformylamino)cyclohexyl]methylthiourea in MeOH and stirred at room temperature overnight. The solvent was removed in vacuo and the residue was dissolved in EtOH. The solution was filtered to remove a white precipitate

and the filtrate was concentrated. The crude product was chromatographed to yield the desired product: 100% yield; 258 (ESMS, MH⁺); ¹H NMR (CD₃OD) δ 8.15 & 8.13 (two s, 1H), 4.15 & 3.73 (two m, 1H), 3.34 & 2.97 (two m, 1H), 3.29 (m, 2H), 1.26 (d, 3H, J=6.7 Hz), 1.23 (d, 3H, J=6.7 Hz), 1.91-1.03 (m, 9H).

Similarly, *N*-[4-(2-methoxyethylformylamino)cyclohexyl]-methylthiourea was prepared: 77% yield, 274 (ESMS, MH⁺); ¹H NMR (CD₃OD) δ 8.15 & 8.00 (two s, 1H), 7.55 & 7.43 (two m, 1H), 3.90 & 2.97 (two m, 1H), 3.46-3.28 (m, 10H), 1.90-0.99 (m, 9H).

General Procedure for the Formation of 2-aminothiazoles Containing a Formamide:

A thiourea such as *N*-[4-(isopropylformylamino)cyclohexyl]-methylthiourea (0.029 mmol, 1 equivalent), a bromoketone (0.044 mmol, 1.5 equivalent) and 2 equivalents of diisopropylethyl amine in 10 ml of EtOH were heated at reflux temperature for 2 days. The reaction mixture was concentrated in vacuo and the crude product chromatographed (silica) to obtain the desired product. This procedure was used to prepare examples 101-102.

A combination of procedures contained in Schemes 6-10 were used to prepare examples 59-100.

Example 59

2-(5-Diethylaminosulfonylamino)pentylamino-4-(2-pyridyl)-thiazole hydrogen chloride was obtained as a brown oil in 2% from *N*¹-[4-(2-pyridinyl)-1,3-thiazol-2-yl]-1,5-pentane-diamine trihydrogen chloride and diethyl sulfamoyl

chloride: ^1H NMR (free base) δ 8.56 (d, 1H, J = 4.5 Hz), 7.89 (d, 1H, J = 8.0 Hz), 7.67 (td, 1H, J = 1.4, 7.8 Hz), 7.72 (s, 1H), 7.16 (m, 1H), 5.66 (m, 1H), 4.57 (t, 1H, J = 6.0 Hz), 3.27 (m, 6H), 2.95 (q, 2H, J = 6.6 Hz), 1.64 (m, 2H), 1.50 (m, 2H), 1.42 (m, 2H), 1.61 (t, 6H, J = 7.1 Hz); ESIMS m/e = 398 (MH^+).

Example 60

4-(2-Pyridyl)-2-(5-(2-thienyl)sulfonylaminopentyl)-amino-thiazole hydrogen chloride was obtained as a yellow solid in 67% from N^1 -[4-(2-pyridinyl)-1,3-thiazol-2-yl]-1,5-pentanediamine trihydrogen chloride and 2-thiophenesulfonyl chloride: m.p. 75-77 °C; ^1H NMR (free base) δ 8.56 (d, 1H, J = 4.6 Hz), 7.86 (dd, 1H, J = 0.5, 7.8 Hz), 7.69 (td, 1H, J = 1.3, 7.7 Hz), 7.61-7.56 (m, 2H), 7.24 (s, 1H), 7.16 (m, 1H), 7.07 (m, 1H), 5.56 (m, 1H), 5.24 (m, 1H), 3.26 (m, 2H), 3.02 (m, 2H), 1.60 (m, 2H), 1.48 (m, 2H), 1.39 (m, 2H); ESIMS m/e = 409 (MH^+).

Example 61

2-(5-(2-Fluorophenyl)sulfonylamino)pentylamino-4-(2-pyridyl)-thiazole hydrogen chloride was obtained as a yellow solid in 81% from N^1 -[4-(2-pyridinyl)-1,3-thiazol-2-yl]-1,5-pentanediamine trihydrogen chloride and 2-fluorobenzenesulfonyl chloride: m.p. 60-63 °C; ^1H NMR (free base) δ 8.57 (dd, 1H, J = 0.7, 4.8 Hz), 7.90 (m, 2H), 7.69 (td, 1H, J = 1.7, 7.8 Hz), 7.57 (m, 1H), 7.20 (m, 3H), 5.46 (m, 1H), 5.13 (m, 1H), 3.24 (q, 2H, J = 6.1 Hz), 2.98 (m, 2H), 1.59 (m, 2H), 1.50 (m, 2H), 1.38 (m, 2H); ESIMS m/e = 421 (MH^+).

Example 62

2-(5-(4-Methoxyphenyl)sulfonylamino)pentylamino-4-(2-pyridyl)thiazole hydrogen chloride was obtained as a light brown solid in 46% from N^1 -[4-(2-pyridinyl)-1,3-thiazol-2-yl]-1,5-pentanediamine trihydrogen chloride and 4-methoxy benzene sulfonyl chloride: m.p. 54-57 °C; ^1H NMR (free base) δ 8.54 (m, 1H), 7.80 (m, 3H), 7.65 (td, 1H, J = 1.7, 7.7 Hz), 7.22 (s, 1H), 7.14 (m, 1H), 6.92 (d, 2H, J = 8.9 Hz), 5.81 (m, 1H), 5.49 (m, 1H), 3.82 (s, 3H), 3.18 (q, 2H, J = 6.0 Hz), 2.86 (q, 2H, J = 6.1 Hz), 1.52 (m, 2H), 1.40 (m, 2H), 1.30 (m, 2H); ESIMS m/e = 433 (MH^+).

Example 63

2-(5-(3,5-Dimethylisoxazol-4-yl)sulfonylamino)pentylamino-4-(2-pyridyl)thiazole hydrogen chloride was obtained as a yellow solid in 87% from N^1 -[4-(2-pyridinyl)-1,3-thiazol-2-yl]-1,5-pentanediamine trihydrogen chloride and 3,5-dimethylisoxazole-4-sulphonyl chloride: ^1H NMR (free base) δ 8.55 (m, 1H), 7.84 (d, 1H, J = 8.0 Hz), 7.69 (td, 1H, J = 1.7, 7.6 Hz), 7.22 (s, 1H), 7.17 (m, 1H), 5.75 (b, 1H), 5.58 (b, 1H), 3.25 (t, 2H, J = 6.4 Hz), 2.93 (t, 2H, J = 6.7 Hz), 2.62 (s, 3H), 2.40 (s, 3H), 1.60 (m, 2H), 1.48 (m, 2H), 1.36 (m, 2H); ESIMS m/e = 422 (MH^+).

Example 64

2-(5-(3,4-Difluorophenyl)sulfonylamino)pentylamino-4-(2-pyridyl)thiazole hydrogen chloride was obtained as a yellow solid in 76% from N^1 -[4-(2-pyridinyl)-1,3-thiazol-2-yl]-1,5-pentanediamine trihydrogen chloride and 3,4-difluorobenzenesulfonyl chloride: m.p. 65-68 °C; ^1H NMR (free base) δ 8.55 (dt, 1H, J = 0.8, 4.8 Hz), 7.84 (d, 1H,

$J = 8.2$ Hz), 7.75-7.63 (m, 3H), 7.33-7.15 (m, 3H), 5.59 (m, 1H), 5.36 (m, 1H), 3.25 (t, 2H, $J = 6.7$ Hz), 2.94 (t, 2H, $J = 6.7$ Hz), 1.60 (m, 2H), 1.48 (m, 2H), 1.37 (m, 2H); ESIMS $m/e = 439$ (MH^+).

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Example 65

2-(5-(2-Methoxy-5-methylphenyl)sulfonylamino)pentylamino-4-(2-pyridyl)thiazole hydrogen chloride was obtained as a pale yellow solid in 69% from N^1 -[4-(2-pyridinyl)-1,3-thiazol-2-yl]-1,5-pentanediamine trihydrogen chloride and 6-methoxy-m-toluene-sulfonyl chloride: m.p. 155-156 °C; 1H NMR (free base) δ 8.57 (m, 1H), 7.88 (d, 1H, $J = 7.9$ Hz), 7.69 (m, 2H), 7.30 (dd, 1H, $J = 1.6, 8.4$ Hz), 7.15 (m, 1H), 6.90 (d, 1H, $J = 8.4$ Hz), 5.40 (m, 1H), 5.04 (m, 1H), 3.91 (s, 3H), 3.24 (q, 2H, $J = 6.4$ Hz), 2.86 (q, 2H, $J = 6.5$ Hz), 2.32 (s, 3H), 1.59 (m, 2H), 1.47 (m, 2H), 1.37 (m, 2H); ESIMS $m/e = 447$ (MH^+).

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Example 66

2-(5-(Benzylsulfonylamino)pentylamino-4-(2-pyridyl)thiazole hydrogen chloride was obtained as a yellow solid in 38% from N^1 -[4-(2-pyridinyl)-1,3-thiazol-2-yl]-1,5-pentane-diamine trihydrogen chloride and α -toluene sulfonyl chloride: m.p. 62-64 °C; 1H NMR (free base) δ 8.56 (dt, 1H, $J = 0.7, 4.8$ Hz), 8.55 (d, 1H, $J = 7.9$ Hz), 7.70 (td, 1H, $J = 1.7, 7.7$ Hz), 7.37 (m, 5H), 7.25 (s, 1H), 7.16 (m, 1H), 5.51 (m, 1H), 4.57 (m, 1H), 4.25 (s, 2H), 3.25 (q, 2H, $J = 6.2$ Hz), 2.94 (q, 2H, $J = 6.4$ Hz), 1.58 (m, 2H), 1.45 (m, 2H), 1.36 (m, 2H); ESIMS $m/e = 417$ (MH^+).

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Example 67

2-(5-(Ethylsulfonylamino)pentyl)amino-4-(2-pyridyl)thiazole hydrogen chloride was obtained as a yellow solid from N^1 -[4-(2-pyridinyl)-1,3-thiazol-2-yl]-1,5-pentanediamine trihydrogen chloride and ethanesulfonyl chloride: m.p. 49-51 °C; ^1H NMR (CD_3OD) δ 8.64 (m, 1H), 8.45-8.35 (m, 2H), 7.84-7.77 (m, 2H), 3.49 (m, 2H), 3.01 (m, 4H), 1.72 (m, 2H), 1.61 (m, 2H), 1.52 (m, 2H), 1.27 (t, 3H, J = 7.4 Hz); ESIMS m/e = 355 (MH^+).

Example 68

2-(5-(Trifluoromethylsulfonylamino)pentyl)amino-4-(2-pyridyl)thiazole hydrogen chloride was obtained as a yellow solid from N^1 -[4-(2-pyridinyl)-1,3-thiazol-2-yl]-1,5-pentanediamine trihydrogen chloride and trifluoromethane sulfonyl chloride: m.p. 63-65 °C; ^1H NMR (CD_3OD) δ 8.76 (m, 1H), 8.62 (m, 1H), 8.40 (m, 1H), 7.96 (m, 1H), 7.80 (m, 1H), 3.28 (m, 2H), 3.19 (m, 2H), 1.74-1.59 (m, 4H), 1.47 (m, 2H); ESIMS m/e = 395 (MH^+).

Example 69

2-(5-(Aminosulfonylamino)pentyl)amino-4-(2-pyridyl)thiazole hydrogen chloride was obtained as a yellow solid from N^1 -[4-(2-pyridinyl)-1,3-thiazol-2-yl]-1,5-pentanediamine trihydrogen chloride and sulfamide: m.p. 68-70 °C; ^1H NMR (CD_3OD) δ 8.46 (dd, 1H, J = 0.6, 4.3 Hz), 7.93 (d, 1H, J = 7.9 Hz), 7.81 (td, 1H, J = 1.7, 7.7 Hz), 7.25 (m, 1H), 7.18 (s, 1H), 3.34 (t, 2H, J = 7.0 Hz), 3.02 (t, 2H, J = 7.0 Hz), 1.65 (m, 2H), 1.60 (m, 2H), 1.47 (m, 2H); ESIMS m/e = 342 (MH^+).

Example 70

2-(5-(2-Fluorophenyl)sulfonylamino)pentylamino-4-(3-pyridyl)thiazole hydrogen chloride was obtained as a yellow solid in 47% from N^1 -[4-(3-pyridinyl)-1,3-thiazol-2-yl]-1,5-pentanediamine trihydrogen chloride and 2-fluorobenzenesulfonyl chloride: m.p. 84-85 °C; ^1H NMR (free base) δ 9.02 (d, 1H, J = 2.1 Hz), 8.51 (m, 1H), 8.05 (dt, 1H, J = 1.5, 7.9 Hz), 7.90 (td, 1H, J = 1.2, 7.3 Hz), 7.55 (m, 1H), 7.32-7.17 (m, 3H), 6.77 (s, 1H), 5.69 (m, 1H), 5.28 (m, 1H), 3.24 (q, 2H, J = 6.4 Hz), 3.00 (q, 2H, J = 6.5 Hz), 1.59 (m, 2H), 1.50 (m, 2H), 1.40 (m, 2H); ESIMS m/e = 420.81 (MH^+).

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Example 71

2-(5-(3,5-Dimethylisoxazol-4-yl)sulfonylamino)pentylamino-4-(3-pyridyl)thiazole hydrogen chloride was obtained as a yellow solid in 41% from N^1 -[4-(3-pyridinyl)-1,3-thiazol-2-yl]-1,5-pentanediamine trihydrogen chloride and 3,5-dimethylisoxazole-4-sulphonyl chloride: m.p. 114-115 °C; ^1H NMR (free base) δ 9.00 (d, 1H), 8.52 (dd, 1H, J = 0.9, 4.6 Hz), 8.01 (m, 1H), 7.30 (dd, 1H, J = 4.9, 8.0 Hz), 6.75 (s, 1H), 6.51-6.44 (m, 2H), 3.18 (q, 2H, J = 6.1 Hz), 2.93 (q, 2H, J = 6.3 Hz), 2.60 (s, 3H), 2.37 (s, 3H), 1.57 (m, 2H), 1.47 (m, 2H), 1.37 (m, 2H); ESIMS m/e = 421.82 (MH^+).

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Example 72

2-(5-(2-Methoxy-5-methyl)phenylsulfonylamino)pentylamino-4-(3-pyridyl)thiazole hydrogen chloride was obtained as a yellow solid in 34% from N^1 -[4-(3-pyridinyl)-1,3-thiazol-2-yl]-1,5-pentanediamine trihydrogen chloride and 6-methoxy-m-toluene-sulfonyl chloride: m.p. 119-120 °C; ^1H NMR (free

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base) δ 9.02 (m, 1H), 8.50 (dt, 1H, J = 0.7, 4.6 Hz), 8.05 (dt, 1H, J = 1.8, 7.9 Hz), 7.69 (d, 1H, J = 2.1 Hz), 7.30 (m, 2H), 6.91 (d, 1H, J = 8.4 Hz), 6.77 (s, 1H), 5.60 (m, 1H), 5.10 (t, 1H, J = 6.4 Hz), 3.92 (s, 3H), 3.24 (q, 2H, J = 6.4 Hz), 2.87 (q, 2H, J = 6.5 Hz), 2.32 (s, 3H), 1.61 (m, 2H), 1.48 (m, 2H), 1.41 (m, 2H); ESIMS m/e = 446.84 (MH+).

Example 73

2-(5-(2-Fluoro)phenylsulfonylamino)pentylamino-4-(4-pyridyl)thiazole hydrogen chloride was obtained as a yellow solid in 44% from N^1 -[4-(4-pyridinyl)-1,3-thiazol-2-yl]-1,5-pentanediamine trihydrogen chloride and 2-fluorobenzenesulfonyl chloride: m.p. 97-98 °C; ^1H NMR (free base) δ 8.57 (d, 2H, J = 5.4 Hz), 7.89 (td, 1H, J = 1.7, 7.7 Hz), 7.63 (d, 2H, J = 5.4 Hz), 7.55 (m, 1H), 7.30-7.17 (m, 2H), 6.93 (s, 1H), 5.52 (m, 1H), 5.26 (m, 1H), 3.25 (q, 2H, J = 6.4 Hz), 2.99 (q, 2H, J = 6.5 Hz), 1.62 (m, 2H), 1.53 (m, 2H), 1.42 (m, 2H); ESIMS m/e = 420.83 (MH+).

Example 74

2-(5-(3,5-Dimethylisoxazol-4-yl)sulfonylamino)pentylamino-4-(4-pyridyl)thiazole hydrogen chloride was obtained as a yellow solid in 36% from N^1 -[4-(4-pyridinyl)-1,3-thiazol-2-yl]-1,5-pentanediamine trihydrogen chloride and 3,5-dimethylisoxazole-4-sulphonyl chloride: m.p. 108-109 °C; ^1H NMR (free base) δ 8.58 (dd, 2H, J = 1.6, 4.7 Hz), 7.63 (dd, 2H, J = 1.5, 4.6 Hz), 6.93 (s, 1H), 5.51 (m, 1H), 5.36 (m, 1H), 3.29 (q, 2H, J = 6.4 Hz), 2.97 (q, 2H, J = 6.4 Hz), 2.62 (s, 3H), 2.39 (s, 3H), 1.64 (m, 2H), 1.53 (m, 2H), 1.42 (m, 2H); ESIMS m/e = 421.81 (MH+).

Example 75

2-(5-(2-Methoxy-5-methyl)phenylsulfonylamino)pentylamino-
4-(4-pyridyl)thiazole hydrogen chloride was obtained as a
5 yellow solid in 29% from N^1 -[4-(4-pyridinyl)-1,3-thiazol-2-
yl]-1,5-pentanediamine trihydrogen chloride and 6-methoxy-
m-toluene-sulfonyl chloride: m.p. 116-117 °C; ^1H NMR (free
base) δ 8.59 (d, 2H, J = 6.0 Hz), 7.71 (d, 1H, J = 1.8
Hz), 7.65 (d, 2H, J = 6.3 Hz), 7.33 (m, 1H), 6.92 (m, 2H),
10 5.16 (m, 1H), 4.88 (m, 1H), 3.94 (s, 3H), 3.29 (q, 2H, J =
6.0 Hz), 2.88 (q, 2H, J = 6.6 Hz), 2.34 (s, 3H), 1.65-1.44
(m, 6H); ESIMS m/e = 446 (MH^+).

Example 76

15 N^1 -{5-[(4-Benzo[b]thiophen-2-yl)-1,3-thiazol-2-yl]amino}-
pentyl}-2-methoxy-5-methyl-1-benzenesulfonamide: 45%
yield; ^1H NMR (CDCl_3) δ 8.22-7.82 (m, 1H), 7.76-7.65 (m,
3H), 7.43-7.27 (m, 4H), 6.86 (d, 1H, J =8.5 Hz), 6.45-6.20
20 (m, 1H), 5.30 (m, 1H), 3.80 (s, 3H), 3.35-3.9 (m, 2H),
2.75 (m, 2H), 2.31 (s, 3H), 1.49-1.29 (m, 6H).

Example 77

25 N^1 -(5-{[4-(5-Chloro-3-methylbenzo[b]thiophen-2-yl)-1,3-
thiazol-2-yl]amino}pentyl)-2-methoxy-5-methyl-1-benzene-
sulfonamide: 55% yield; Anal. Calc. for $\text{C}_{25}\text{H}_{28}\text{ClN}_3\text{S}_3\text{O}_3 + 0.3$
 CH_2Cl_2 : C, 52.80; H, 5.00; N, 7.10. Found: C, 53.23; H,
4.68; N, 6.82; ^1H NMR (CDCl_3) δ 7.75-7.65 (m, 3H), 7.30-
30 7.25 (m, 2H), 6.91 (d, 1H, J =7.50 Hz), 6.65 (s, 1H), 5.28-
5.20 (m, 1H), 4.95-4.85 (m, 1H), 3.95 (s, 3H), 3.35-3.25
(m, 2H), 2.95-2.85 (m, 2H), 2.55 (s, 3H), 2.35 (m, 3H),
2.65-1.25 (m, 6H).

Example 78

N1-(4-{[4-(5-Phenyl-3-isoxazolyl)-1,3-thiazol-2-yl]amino}-
pentyl)-2-methoxy-5-methyl-1-benzenesulfonamide: 40%

5 yield: Anal. Calc. for $C_{25}H_{28}N_4S_2O_4 + 0.30 CH_3COOC_2H_5$: C, 58.40;
H, 5.60; N, 10.30. Found: C, 58.50; H, 5.51; N, 10.10. 1H
NMR ($CDCl_3$) δ 7.90-7.82 (m, 2H), 7.75-7.65 (m, 1H), 7.55-
7.42 (m, 3H), 7.35-7.25 (m, 1H), 7.10 (s, 1H), 6.92-6.85
(m, 1H), 6.80 (s, 1H), 5.45-5.42 (m, 1H), 5.05-5.00 (m,
10 1H), 3.90 (s, 3H), 3.40-3.20 (m, 2H), 2.95-2.82 (m, 2H),
2.35 (s, 3H), 1.75-1.35 (m, 6H).

Example 79

15 N1-(5-{[4-(3-Thienyl)-1,3-thiazol-2-yl]amino}pentyl)-2-
methoxy-5-methyl-1-benzenesulfonamide: 45% yield; 1H NMR
($CDCl_3$) δ 7.82-7.75 (m, 2H), 7.70 (s, 1H), 7.55-7.30 (m,
3H), 6.95-6.85 (d, 1H, $J=7.5$ Hz), 6.35-6.25 (m, 1H), 5.12-
5.05 (m, 1H), 3.90 (s, 3H), 3.45-3.35 (m, 2H), 2.92-2.82
20 (m, 2H), 2.35 (s, 3H), 1.60-1.35 (m, 6H).

Example 80

25 N1-[5-({4-[1-(Phenylsulfonyl)-1H-3-pyrrolyl]-1,3-thiazol-
2-yl}amino)pentyl]-2-methoxy-5-methyl-1-
benzenesulfonamide: 43% yield: 1H NMR ($CDCl_3$) δ 7.80-7.95
(m, 1H), 7.60-7.91 (m, 2H), 7.35-7.45 (m, 5H), 7.15-7.05
(m, 2H), 6.95 (s, 1H), 6.75 (s, 1H), 4.60-4.15 (broad,
2H), 3.80 (s, 3H), 2.35-3.25 (m, 2H), 2.85-2.65 (m, 2H),
30 2.25 (s, 3H), 1.55-1.22 (m, 6H).

Example 81

trans-N8-[(4-{[4-(3-Phenyl-5-isoxazolyl)-1,3-thiazol-2-yl]amino}cyclohexyl)methyl]-8-quinolinesulfonamide:

5 3.5% yield, 546 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 9.04 (dd, 1H, J=1.7, 4.5 Hz), 8.45 (dd, 1H, J=0.6, 7.6 Hz), 8.31 (apparent td, 1H, J=1.8, 8.3 Hz), 8.09 (apparent td, 1H, J=1.8, 8.2 Hz), 7.84(m, 1H), 7.68 (apparent dt, 1H, J=1.5, 7.7 Hz), 7.62-7.57 (m, 1H), 7.52-7.41 (m, 3H), 7.06 (s, 1H), 6.81 (s, 1H), 6.5-6.4 (m, 1H), 5.13 (d, 1H, J=8.2 Hz), 4.29 (b, 1H), 3.27 (m, 1H), 2.71 (apparent dt, 2H, J=3.1, 6.6 Hz), 2.21-0.94 (m, 9H).

Example 82

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N,N-Dimethyl-N'-(5-{[4-(3-Thienyl)-1,3-thiazol-2-yl]amino}pentyl)sulfamide: 45% yield; Anal. Calc. for C₁₄H₂₂N₄S₃O₂: C, 44.90; H, 5.70; N, 14.90. Found: C, 44.60; H, 5.77; N, 14.47. ¹H NMR (CDCl₃) δ 7.59 (d, J=4.5 Hz), 7.37-7.26 (m, 2H), 6.55 (s, 1H), 5.60-5.58 (broad, 1H), 4.63-4.50 (m, 1H), 3.28-3.21 (m, 2H), 3.07-2.99 (m, 2H), 2.80 (s, 3H), 1.79-1.37 (m, 6H).

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Example 83

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trans-2-(4-(2-Methoxy-5-methylphenyl)sulfonylamino)-cyclohexylmethylamino-4-(2-pyridyl)thiazole dihydrogen chloride was obtained as a yellow solid in 7% from N-[(4-aminocyclohexyl)methyl]-4-(2-pyridinyl)-1,3-thiazol-2-amine and 6-methoxy-m-toluene-sulfonyl chloride: m.p. 111-113° C; ¹H NMR (CD₃OD) δ 8.39 (m, 1H), 7.74 (m, 2H), 7.60 (s, 1H), 7.40 (m, 3H), 7.04 (dd, 1H, J = 1.2, 8.2 Hz), 3.90 (s, 3H), 3.32 (m, 2H), 2.93 (m, 1H), 2.31 (s, 3H),

30

1.71 (m, 4H), 1.53 (m, 1H), 1.28 (m, 2H), 0.90 (m, 2H);
ESIMS m/e = 473.1 (MH⁺).

Example 84

5

trans-2-(4-(2-Fluorophenyl)sulfonylamino)cyclohexylmethyl-
amino-4-(2-pyridyl)thiazole dihydrogen chloride was
obtained as a yellow solid in 5% from *N*-[(4-
aminocyclohexyl)methyl]-4-(2-pyridinyl)-1,3-thiazol-2-
10 amine and 2-fluorobenzene sulfonyl chloride: m.p. 113-115
°C; ¹H NMR (CD₃OD) δ 8.40 (m, 1H), 7.88-7.71 (m, 3H), 7.60
(m, 1H), 7.43 (m, 2H), 7.30 (m, 2H), 3.33 (m, 2H), 3.09
(m, 1H), 1.78 (m, 4H), 1.53 (m, 1H), 1.42-1.24 (m, 2H),
0.90 (m, 2H); ESIMS m/e = 473.2 (MH⁺).

15

Example 85

trans-2-(4-(3,5-Dimethyl-4-isoxazolyl)sulfonylamino)-
cyclohexylmethylamino-4-(2-pyridyl)thiazole dihydrogen
20 chloride was obtained as a yellow solid in 7% from *N*-[(4-
aminocyclohexyl)methyl]-4-(2-pyridinyl)-1,3-thiazol-2-
amine and 3,5-dimethylisoxazole-4-sulfonyl chloride: m.p.
98-101 °C; ¹H NMR (CD₃OD) δ 8.40 (m, 1H), 7.79 (m, 2H),
7.45 (m, 2H), 3.33 (m, 2H), 2.99 (m, 1H), 2.59 (s, 3H),
25 2.38 (s, 3H), 1.81 (m, 4H), 1.58 (m, 1H), 1.30 (m, 2H),
0.90 (m, 2H); ESIMS m/e = 448.2 (MH⁺).

Example 86

30

trans-2-(4-(2-Fluorophenyl)sulfonylamino)cyclohexylmethyl-
amino-4-(3-pyridyl)thiazole dihydrogen chloride was
obtained as a grayish solid in 7% from *N*-[(4-
aminocyclohexyl)methyl]-4-(3-pyridinyl)-1,3-thiazol-2-
amine and 2-fluorobenzene sulfonyl chloride: m.p. 141-142

°C; ¹H NMR (free base) δ 9.01 (s, 1H), 8.50 (d, 1H, *J* = 4.6 Hz), 8.03 (d, 1H, *J* = 7.9 Hz), 7.91 (td, 1H, *J* = 1.2, 7.4 Hz), 7.56 (m, 1H), 7.31-7.7.17 (m, 3H), 6.75 (s, 1H), 5.62 (b, 1H), 4.90 (b, 1H), 3.17 (m, 1H), 3.11 (t, 2H, *J* = 6.1 Hz), 1.92-1.79 (m, 4H), 1.56 (m, 1H), 1.20 (m, 2H), 1.01 (m, 2H); ESIMS *m/e* = 447.1 (MH⁺).

Example 87

10 *trans*-2-(4-(2-Methoxy-5-methylphenyl)sulfonylamino)-
cyclohexylmethylamino-4-(4-pyridyl)thiazole dihydrogen
chloride was obtained as a brownish solid in 4% from *N*-
[(4-aminocyclohexyl)methyl]-4-(4-pyridinyl)-1,3-thiazol-2-
amine and 6-methoxy-*m*-toluene-sulfonyl chloride: ¹H NMR
15 (CD₃OD) δ 8.71 (dd, 2H, *J* = 1.2, 6.9 Hz), 8.37 (dd, 2H, *J* =
1.2, 7.0 Hz), 7.89 (s, 1H), 7.62 (s, 1H), 7.38 (m, 1H),
7.05 (d, 1H, *J* = 8.6 Hz), 3.90 (s, 3H), 3.24 (m, 2H), 2.95
(m, 1H), 2.31 (s, 3H), 1.76 (m, 4H), 1.57 (m, 1H), 1.30
(m, 2H), 0.98 (m, 2H); ESIMS *m/e* = 473.2 (MH⁺).

20

Example 88

*N*1-(5-[4-(1,3-thiazol-2-yl)-1,3-thiazol-2-yl]aminopentyl)-
2-methoxy-5-methyl-1-benzenesulfonamide: Anal. Calc. for
25 C₁₉H₂₄N₄S₃O₃+1.00 CH₃COOC₂H₅: C, 51.50; H, 5.90; N, 10.30.
Found: C, 51.69; H, 5.60; N, 10.30. ¹H NMR (CDCl₃) δ 7.75
(s, 1H), 7.66 (s, 1H), 7.44-7.25 (m, 3H), 6.88 (d, 1H,
J=8.3 Hz), 5.67-5.64 (m, 1H), 5.20-5.15 (m, 1H), 3.89 (s,
3H), 3.73-3.17 (m, 2H), 2.87-2.81 (m, 2H), 2.30 (s, 3H),
30 1.80 1.25 (m, 6H).

Example 89

trans-N1-[(4-[4-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminocyclohexyl)methyl]-2-methoxy-5-methyl-1-benzenesulfonamide: 11% yield, 507 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 7.70 (d, 1H, J=2.1 Hz), 7.33 (dd, 1H, J=2.0, 8.8 Hz), 6.93 (d, 1H, J=8.5 Hz), 6.43 (s, 1H), 5.06 (m, 1H), 4.95 (m, 1H), 3.95 (s, 3H), 3.24 (m, 1H), 2.71 (t, 2H, J=6.7 Hz), 2.64 (s, 3H), 2.55 (s, 3H), 2.34 (s, 3H), 2.03 (ABm, 4H), 1.47 (m, 1H), 1.26-0.97 (m, 4H).

Example 90

trans-N,N-dimethyl-N'-[(4-[4-(-1,3-thiazol-2-yl)-1,3-thiazol-2-yl]aminocyclohexyl)methyl]sulfamide: 12.3% yield, 402 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 7.80 (d, 1H, J=3.3 Hz), 7.29 (d, 1H, J=3.1 Hz), 7.19 (s, 1H), 5.16 (d, 1H, J=8.2 Hz), 4.14 (b, 1H), 3.30 (m, 1H), 2.95 (t, 2H, J=6.6 Hz), 2.81 (s, 6H), 2.09 (ABm, 4H), 1.51 (m, 1H), 1.30-0.85 (m, 4H).

Example 91

N,N-Dimethyl-N'-(5-{[4-(2-thienyl)-1,3-thiazol-2-yl]amino}-pentyl)sulfamide: 45% Yield; ¹H NMR (CDCl₃) δ 7.30 (d, 1H, J=4.5 Hz), 7.20 (d, 1H, J=4.5 Hz), 7.05-6.95 (m, 1H), 6.55 (s, 1H), 6.35-6.25 (m, 1H), 5.55-5.45 (m, 1H), 3.20-3.10 (m, 2H), 3.00-2.9 (m, 2H), 2.80 (s, 6H), 1.60-1.25 (m, 6H).

Example 92

N1-(5-{[4-(2-Thienyl)-1,3-thiazol-2-yl]amino}pentyl)-2-methoxy-5-methyl-1-benzenesulfonamide: 40% Yield; ^1H NMR (CDCl₃) δ 7.67 (s, 1H), 7.30-7.27 (m, 2H), 7.15 (d, 1H, J=4.3 Hz), 6.99-6.95 (m, 1H), 6.87 (d, 1H, J=8.3 Hz), 6.52 (s, 1H), 5.92 (broad, 1H), 5.36-5.31 (m, 1H), 3.88 (s, 3H), 3.15-3.11 (m, 2H), 2.85-2.78 (m, 2H), 2.30 (s, 3H), 1.54-1.30 (m, 6H).

Example 93

N1-(5-[4-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminopentyl)-2-methoxy-5-methyl-1-benzenesulfonamide: 40% Yield; Anal. Calc. For C₂₁H₂₈N₄S₃O₃+0.20 CH₃COOC₂H₅: C, 52.61; H, 6.00; N, 11.10. Found: C, 52.96; H, 5.93; N, 10.92; ^1H NMR (CDCl₃) δ 7.70 (d, 1H, J=4.3 Hz), 7.33-7.30 (m, 1H), 9.91 (d, 1H, J=8.3 Hz), 6.43 (s, 1H), 5.28 (broad, 1H), 4.99-4.95 (m, 1H), 3.92 (s, 3H), 3.24-3.18 (m, 2H), 2.90-2.83 (m, 2H), 2.63 (s, 3H), 2.54 (s, 3H), 2.32 (s, 3H), 1.64-1.34 (m, 6H).

Example 94

N1-(5-[4-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminopentyl)-4-fluoro-1-benzenesulfonamide: 40% Yield; Anal. Calc. for C₁₉H₂₃F₁N₄S₃O₂+0.3CH₃COOC₂H₅: C, 50.50; H, 5.30; N, 11.60. Found: C, 50.71; H, 4.92; N, 11.25. ^1H NMR (CDCl₃) δ 7.85 (q, 2H, J=4.3 Hz), 7.14 (t, 2H, J=7.5 Hz), 6.41 (s, 1H), 8.84-5.80 (m, 1H), 5.65 (t, 1H, J=4.3 Hz), 3.20-3.13 (m, 2H), 2.92-2.85 (m, 2H), 2.59 (s, 3H), 2.50 (s, 3H), 1.53-1.29 (m, 6H).

Example 95

N1-(5-[4-(1,3-Thiazol-2-yl)-1,3-thiazol-2-yl]aminopentyl)-
4-fluoro-1-benzenesulfonamide: 40% Yield; Anal. Calc. for
5 C₁₇H₁₉F₁N₄S₃O₂: C, 51.52; H, 4.79; N, 11.01. Found: C, 51.41,
H, 5.57; N, 10.60. ¹H NMR (CDCl₃) δ 7.95-7.85 (m, 2H),
7.80-7.70 (m, 1H), 7.60-7.40 (m, 1H), 7.3 (d, 1H, J=4.3
Hz), 7.20-7.10 (m, 2H), 5.60-5.45 (m, 1H), 5.20-5.00 (m,
2H), 3.45-3.20 (m, 2H), 3.00-2.80 (m, 2H), 1.80-1.25 (m,
10 6H).

Example 96

N'-(5-[4-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-
15 yl]aminopentyl)-N,N-dimethylsulfamide: 35% Yield; Anal.
Calc. for C₁₅H₂₅N₄S₃O₂: C, 44.85; H, 6.31; N, 16.90. Found:
C, 44.74; H, 6.38; N, 16.61. ¹H NMR (CDCl₃) δ 7.88 6.40 (s,
1H), 6.00-5.95 (m, 1H), 5.35-5.20 (m, 1H), 3.25-3.15 (m,
2H), 3.05-2.95 (m, 2H), 2.80 (s, 6H), 2.60 (s, 3H), 2.50
20 (s, 3H), 1.60-1.25 (m, 6H).

Example 97

trans-N1-[(4-[4-(2,5-dimethyl-1,3-thiazol-4-yl)]-1,3-
25 thiazol-2-yl]aminocyclohexyl)methyl]-4-fluoro-1-benzene-
sulfonamide: 99% yield, 481 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ
7.88 (m, 2H), 7.20 (t, 2H, J=8.2 Hz), 6.42 (s, 1H), 5.23
(b, 1H), 5.11-4.81 (b, 1H), 3.21 (m, 1H), 2.80 (t, 2H,
J=6.0 Hz), 2.62 (s, 3H), 2.53 (s, 3H), 2.00 (ABm, 4H),
30 1.42 (m, 1H), 1.24-0.96 (m, 4H).

Example 98

trans-N'-[(4-[4-(2,5-dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminocyclohexyl)methyl]-*N,N*-dimethylsulfamide: 45% yield, 430 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 6.44 (s, 1H), 5.13 (d, 1H, J=7.9 Hz), 4.26 (t, 1H, J=6.9 Hz), 3.27 (m, 1H), 2.93 (t, 2H, J=6.6 Hz), 2.81 (s, 6H), 2.64 (s, 3H), 2.55 (s, 3H), 2.07 (ABm, 4H), 1.51 (m, 1H), 1.30-1.03 (m, 4H).

Example 99

trans-N'-[4-([5-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminomethyl)cyclohexyl]methyl-*N,N*-dimethylsulfamide: 45% Yield; ¹H NMR (CDCl₃) δ 6.40 (s, 1H), 5.82-5.70 (m, 1H), 4.82-4.75 (m, 1H), 3.20-3.05 (m, 2H), 3.00-2.82 (m, 2H), 2.80 (s, 6H), 2.60 (s, 3H), 2.50 (s, 3H), 1.85-1.35 (m, 8H), 1.05-0.82 (m, 2H).

Example 100

trans-N4-[4-([4-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminomethyl)cyclohexyl]methyl-4-morpholine-sulfonamide: 40% Yield; Anal. Calc. for C₂₀H₃₁N₄S₃O₃: C, 49.40; H, 6.40; N, 14.40. Found: C, 49.19; H, 6.47; N, 13.92. ¹H NMR (CDCl₃) δ 6.40 (s, 1H), 6.00-5.85 (m, 1H), 5.30-5.15 (m, 1H), 3.80-3.60 (m, 4H), 3.20-2.82 (m, 8H), 2.6 (s, 3H), 2.50 (s, 3H), 1.80-1.18 (m, 8H), 1.05-0.82 (m, 2H).

Example 101

trans-N-[4-([4-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminomethyl)cyclohexyl]-*N*-(2-

methoxyethyl)formamide: 33% yield, 409 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.18 & 8.08 (two s, 1H), 6.44 (s, 1H), 5.32 (b, 1H), 3.48 (two s, 3H), 3.46-3.39 (m, 4H), 3.34 & 3.33 (two d, 2H, J=2.6 Hz), 3.15 (m, 1H), 2.64 (s, 3H), 2.550 & 2.548 (two s, 3H), 2.00-0.83 (m, 9H).

Example 102

trans-N-[4-([4-(2,5-Dimethyl-1,3-thiazol-4-yl)-1,3-thiazol-2-yl]aminomethyl)cyclohexyl]-*N*-isopropylformamide: 59% yield, 393 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.20 & 8.18 (two s, 1H), 6.44 (s, 1H), 5.43 (b, 1H), 4.29 & 3.60 (two m, 1H), 3.74 (m, 1H), 3.13 (m, 2H), 2.64 (s, 3H), 2.54 (s, 3H), 1.27 (dd, 3H, J=1.2, 7.0 Hz), 1.21 (dd, 3H, J=1.2, 7.0 Hz), 1.98-1.06 (m, 9H).

I. Synthetic Methods for ExamplesC. Tricyclic Compounds5 **General Procedures Relating to Examples:**

For the formation of 2-aminothiazoles from 2-haloketones and thioureas, see, for example, Kearney, P.C., et al., 1998; Di Fabio, R. and Pentassuglia, G., 1998; De Kimpe, N., et al., 1996; Plazzi, P.V., et al., 1995; and
10 Novikova, A. P., 1991.

For the formation of thiazoles from 2-haloketones and thioamides, see, for example, Critcher, D. J. and Pattenden, G., 1996; and Friedman, B. S., et al., 1937.

15

For the formation of 2-aminoimidazoles from 2-haloketones and guanidines, see, for example, Little, T. L. and Webber, 1994; and Chabaka, L.M., et al., 1994.

20

For the formation of imidazoles from 2-haloketones and amidines, see, for example, Demchenko, A. M., et al., 1997; and Nagao, Y., et al., 1996.

25

For the synthesis of 2-aminooxazoles from 2-haloketones and ureas, see, for example, Pathak, V.N., et al., 1993; Crangk, G. and Foulis, M.J., 1971; and Marchetti, E., et al., 1968.

30

For the formation of oxazoles from 2-haloketones and amides, see, for example, Hammar, W.J. and Rustad, M.A., 1981; and Zhao, Z., et al., 1991.

All reactions were performed under an inert atmosphere (Argon) and the reagents, neat or in appropriate solvents,

were transferred to the reaction vessel via syringe and cannula techniques. The parallel synthesis reaction arrays were performed in vials (without an inert atmosphere) using J-KEM heating shakers (Saint Louis, MO).

5 Unless stated otherwise all solvents were AR grade and used as supplied. Anhydrous solvents were purchased from Aldrich Chemical Company and used as received. Examples 1-64 described in this patent application were named using ACD/Name program (version 2.51, Advanced Chemistry
10 Development Inc., Toronto, Ontario, M5H2L3, Canada).

^1H and ^{13}C spectra were recorded at 300 and 75 MHz (QE Plus) with CDCl_3 as solvent (unless otherwise noted) and tetramethylsilane as internal standard. s = singlet; d =
15 doublet; t = triplet; q = quartet; p = pentet; sextet; septet; b = broad; m = multiplet. Elemental analyses were performed by Robertson Microlit Laboratories, Inc. Low-resolution electrospray MS spectra were measured (ESMS, MS) and MH^+ is reported. Thin-layer chromatography (TLC)
20 was carried out on glass plates precoated with silica gel 60 F₂₅₄ (0.25 mm, EM Separations Tech.). Preparative thin-layer chromatography was carried out on glass sheets precoated with silica gel GF (2 mm, Analtech). Flash column chromatography was performed on Merck silica gel 60
25 (230 - 400 mesh). Melting points were determined in open capillary tubes on a Med-Temp apparatus and are uncorrected.

General Procedure for the Synthesis of Benzothiepin-5-ones:

2,3,4,5-Tetrahydro-1-benzothiepin-5-one:

5 Step 1.

4-(phenylsulfanyl)butanoic acid:

Sodium methoxide (1.2 equivalent) was added to 60 ml of ethanol, in one portion, and the suspension was stirred at
10 room temperature. Thiophenol (1 equivalent) was added to the above suspension and stirred at room temperature for 30 minutes. Butyrolactone (1.1 equivalent) was added to the reaction mixture and the resulting mixture was stirred at reflux temperature for 6 hours, cooled to room
15 temperature and concentrated in vacuo. The resulting solid was washed with 200 ml hexane/ether 2:1, v/v. The solid was suspended into ice cold 2N HCl solution and stirred for 15 minutes. The resulting solid was filtered, washed with 100 ml hexane/ether and dried under reduced pressure
20 at room temperature to give 4-(phenylsulfanyl)butanoic acid as tan solid: 52% yield; ^1H NMR (CDCl_3) δ 7.32-7.12 (m, 5H), 2.94 (t, 2H, $J=7.2$ Hz), 2.41 (t, 2H, $J=7.2$ Hz), 1.85 (p, 2H, $J=7.2$ Hz); Anal. Calc. For $\text{C}_{10}\text{H}_{12}\text{S}_1\text{O}_2$: C, 61.22; H, 6.12. Found: C, 61.16; H, 6.28.

25 A similar procedure was used for the synthesis of 4-(4-fluorophenylsulfanyl)butanoic acid: 60% yield; ^1H NMR (CDCl_3) δ 7.34 (m, 2H, 7.00 (m, 2H), 2.94 (t, 2H, $J=7.2$ Hz), 2.51 (t, 2H, $J=7.2$ Hz), 1.93 (p, 2H, $J=7.2$ Hz); Anal.
30 Calc. For $\text{C}_{10}\text{H}_{11}\text{F}_1\text{S}_1\text{O}_2$: C, 56.07; H, 5.14. Found: C, 55.80; H, 5.19.

Step 2.

Benzothiepin-5-ones:

5 Polyphosphoric acid (6 equivalents) was heated to 80°C under argon. 4-(Phenylsulfanyl)butanoic acid from the step above, (1 equivalent) was added in portions and the mixture was kept at 100°C for 2 hours. The reaction mixture was cooled, dropped into ice cold water and extracted with 2X100 ml ethyl acetate. The combined ethyl acetate
10 extracts were washed with 100 ml water, 100 ml saturated sodium bicarbonate, and 100 ml water. The ethyl acetate extract was dried (anhydrous sodium sulfate), filtered and the solvent removed in vacuo to give a tan solid. The solid was dried under vacuum to give 2,3,4,5-tetrahydro-1-benzothiepin-5-one: 52% yield; ¹H NMR (CDCl₃) δ 7.824 (dd, 1H, J=0.9, 7.5 Hz), 7.45 (dd, 1H, J=0.6, 6.9 Hz), 7.34-7.21 (m, 2H), 3.05 (t, 2H, J=6.6 Hz), 2.97 (t, 2H, J=6.6 Hz), 2.29 (p, 2H, J=6.6 Hz).

20 The above described procedure was also used to give 7-fluoro-2,3,4,5-tetrahydro-1-benzothiepin-5-one: 60% yield; ¹H NMR (CDCl₃) δ 7.51 (dd, 1H, J=3.0, 9.3 Hz), 7.41 (dd, 1H, J=8.7, 5.1 Hz), 7.04 (apparent dt, 1H, J=3.0, 4.8 Hz), 3.06 (t, 2H, J=6.6 Hz), 2.96 (t, 2H, J=6.6 Hz), 2.64 (t, 2H, J=6.9 Hz); Anal. Calc. For C₁₀H₁₀S₁O₁: C, 67.41; H, 5.61. Found: C, 67.48; H, 5.68.

General Procedure for the Synthesis of Bromoketones:

30

To the solution of the ketone (1 equivalent) in acetic acid, cooled in a water bath, was added bromine (1 equivalent) slowly. The reaction mixture was stirred at room temperature for 3 hours. Solvents were evaporated,

the residue was dissolved in dichloromethane and the resultant solution washed with saturated sodium bicarbonate and water and dried over sodium sulfate. Evaporation of the combined decolorized organic phase afforded the desired product as a light yellow oil in more than 80% yield in most cases.

7-Fluoro-2,3,4,5-tetrahydro-1-benzothiepin-5-one was brominated according to the procedure described below to give 4-bromo-7-fluoro-2,3,4,5-tetrahydro-1-benzothiepin-5-one. A similar procedure was also used to brominate 2,3,4,5-tetrahydro-1-benzothiepin-5-one.

4-Bromo-7-fluoro-2,3,4,5-tetrahydro-1-benzothiepin-5-one:

7-Fluoro-2,3,4,5-tetrahydro-1-benzothiepin-5-one (1 equivalent) was dissolved in glacial acetic acid and stirred at room temperature. Bromine (2.5 equivalents) was added to the above mixture dropwise and stirring continued at room temperature for 4 hours. Water was added to the reaction mixture and the mixture was then extracted with 2x25 ml ethyl acetate. The combined ethyl acetate extracts were washed with water, saturated sodium bicarbonate, and water. The combined ethyl acetate extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford a solid which was re-crystallized from ethyl acetate/hexane 1:1 v/v to afford 4-bromo-7-fluoro-2,3,4,5-tetrahydro-1-benzothiepin-5-one: ^1H NMR (CDCl_3) δ 7.55 (dd, 1H, $J=2.7, 9.0$ Hz), 7.44 (dd, 1H, $J=8.7, 5.1$ Hz), 7.11 (Apparent dt, 1H, $J=2.7, 4.8$ Hz), 5.34 (dd, 1H, $J=5.7, 10.2$ Hz), 3.20-2.50 (m, 4H).

4-bromo-2,3,4,5-tetrahydro-1-benzothiepin-5-one: ^1H NMR (CDCl_3) δ 7.83 (d, 1H, $J=7.8$ Hz), 5.35 (dd, 1H, $J=5.7, 10.5$ Hz), 3.30-2.50 (m, 4H).

General Procedure for the Synthesis of Boc Protected Thioureas:

5 A protected diamine such as N-Boc-1,4-diaminobutane or N-Boc-1,5-diaminopentane (1 equivalent) was dissolved in tetrahydrofuran and stirred at room temperature. Benzoyl thioisocyanate (1 equivalent) was added dropwise to the
10 aforementioned solution. The resulting mixture was stirred at room temperature for 24 hours. The solvent was removed under reduced pressure to give a yellow oil. The yellow oil (1 equivalent) from the above step was dissolved in methanol, an aqueous potassium carbonate (3 equivalents) solution was added, and the mixture stirred for 48 hours.
15 Water was added to the reaction mixture, which was then extracted with 2x75 ml ethyl acetate. The combined ethyl acetate extracts were washed with water, dried with anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to give the desired thiourea.

20 *tert*-Butyl 5-[(aminocarbothioyl)amino]pentylcarbamate was obtained as a light yellow wax from *tert*-butyl 5-[[*N*-(benzoylamino)carbothioyl]amino]-pentylcarbamate. ¹H NMR (CD₃OD) δ 3.44 (m, 1H), 3.10 (m, 1H), 3.01 (t, 2H, *J* = 6.7
25 Hz), 1.60-1.31 (m, 6H), 1.41 (s, 9H); 262 (ESMS, MH⁺).

tert-Butyl 5-[[*N*-(benzoylamino)carbothioyl]amino]-pentylcarbamate was obtained as a light yellow solid in 79% yield from *N*-BOC-1,5-diaminopentane and benzoyl
30 isothiocyanate; m.p. 90-93 °C.

tert-Butyl 4-[(aminocarbothioyl)amino]butylcarbamate was obtained as a light yellow wax from *tert*-butyl 4-[[*N*-(benzoylamino)carbothioyl]amino]-butylcarbamate. ¹H NMR

(CD₃OD) δ 3.48 (m, 1H), 3.10 (m, 1H), 3.05 (t, 2H, J = 6.5 Hz), 1.60 (m, 4H), 1.42 (s, 9H); 248 (ESMS, MH⁺).

Tert-Butyl 4-{[(benzoylamino)carbothioyl]amino} butylcarbamate was obtained as a light brown oil in 93% yield from N-BOC-1,4-diaminobutane and benzoyl isothiocyanate.

trans-tert-Butyl {4-[(aminocarbothioyl)amino]cyclohexyl}methylcarbamate was obtained as a light yellow wax from trans-tert-butyl (4-{[(benzoylamino)carbothioyl]amino}cyclohexyl)-methylcarbamate. ¹H NMR (CD₃OD) δ 3.92 (m, 1H), 2.86 (m, 2H), 2.00 (m, 2H), 1.76 (m, 2H), 1.41 (s, 9H), 1.37 (m, 1H), 1.06 (m, 4H); 288 (ESMS, MH⁺).

trans-tert-Butyl (4-{[(benzoylamino)carbothioyl]amino}cyclohexyl)-methylcarbamate was obtained as a yellow solid in 97% yield from tert-butyl 4-aminocyclohexylmethylcarbamate and benzoyl isothiocyanate.

trans-tert-Butyl 4-Aminocyclohexylmethylcarbamate was obtained in more than 95 % yield from hydrogenation of benzyl 4-{[(tert-butoxycarbonyl)amino]methyl} cyclocarbamate.

Benzyl-4-[[[tert-butoxycarbonyl]amino]methyl]cyclohexylcarbamate: To a stirred suspension of 4-[[[tert-butoxycarbonyl]amino]methyl]cyclohexanecarboxylic acid (Maybridge Chemical Co., Ltd.) (45g) and diphenylphosphoryl azide (44 ml) in toluene (600 ml) was added triethylamine (32 ml) over a period of 20 min whilst maintaining the internal temperature at -10-0 C. The mixture was slowly warmed and then stirred at

70 C for 4 h. After cooling to 40 C, benzyl alcohol (36 ml) was added and the reaction mixture heated at reflux for 20 h. The cold reaction mixture was washed with water and brine and dried over anhydrous magnesium sulfate. Removal of the solvent and recrystallization of the organic residue from ethyl acetate and diethyl ether gave the title compound, benzyl-4-[[[tert-butoxycarbonyl]amino]methyl]cyclohexylcarbamate as a white solid, m.p. 129-131 C.

trans-tert-Butyl 4-{[(aminocarbothioyl)amino]cyclohexyl}carbamate was obtained as a yellow solid from *trans*-tert-butyl 4-{[(benzoylamino)carbothioyl]amino}cyclohexyl)-carbamate: ¹H NMR (CD₃OD) δ 3.94 (m, 1H), 3.30 (m, 1H), 2.00 (m, 2H), 1.90 (m, 2H), 1.41 (s, 9H), 1.26 (m, 4H); 274 (ESMS, MH⁺).

trans-tert-Butyl 4-{[(Benzoylamino)carbothioyl]amino}cyclohexyl)-carbamate was obtained as a white solid in 66% yield from *tert*-butyl 4-aminocyclohexylcarbamate and benzoyl isothiocyanate.

trans-tert-Butyl 4-aminocyclohexylcarbamate was obtained as a light yellow wax in more than 95% yield by hydrogenation of benzyl 4-[(tert-butoxycarbonyl)amino]cyclohexylcarbamate.

trans-Benzyl 4-{[(aminocarbothioyl)amino]methyl}cyclohexylcarbamate was obtained as a yellow solid in 71% yield from *trans*-benzyl 4-({[(Benzoylamino)carbothioyl]amino}methyl)-cyclohexylcarbamate; 322 (ESMS, MH⁺).

trans-Benzyl 4-({[(Benzoylamino)carbothioyl]amino}

methyl)-cyclohexylcarbamate was obtained as a yellow solid from benzyl 4-(aminomethyl)cyclohexylcarbamate and benzoyl isothiocyanate.

5 trans-benzyl 4-(aminomethyl)cyclohexylcarbamate was
obtained as a white solid in more than 95% yield by
stirring benzyl-4-{[(tert-butoxycarbonyl)amino]-
methyl}cyclocarbamate in 2N HCl (made from 1 : 1 of EtOAc
and 4N HCl in dioxane).

10

**General Procedure for the Synthesis of the (4,5-
dihydrobenzo[2,3]thiepin[4,5-d][1,3]thiazol-2-ylamino
Template:**

15 A mixture of a bromoketone such as 7-fluoro-2,3,4,5-
tetrahydro-1-benzothiepin-5-one (1 equivalent), a thiourea
(1 equivalent), and diisopropylethylamine (2 equivalents)
in anhydrous ethanol was stirred and heated at reflux
temperature overnight. The solvent was evaporated, the
20 brown residue dissolved in dichloromethane and the
resultant solution washed with saturated aqueous sodium
bicarbonate. The aqueous phase was extracted with
dichloromethane three times. The combined extracts were
dried over anhydrous sodium sulfate. The crude product was
25 purified by flash column chromatography (Silica Gel,
hexanes : ethyl acetate). An example of the aforementioned
general procedure follows.

30 4-Bromo-2,3,4,5-tetrahydro-1-benzothiepin-5-one (1.2
equivalent, 29.76 mmol) and tert-butyl 5-
[(aminocarbothioyl)amino]pentylcarbamate (1 equivalent,
24.8 mmol) were mixed with 2 equivalents diisopropylethyl
amine in 200 ml of EtOH. The reaction mixture was heated
at reflux temperature overnight. The dark brown reaction

mixture was concentrated and chromatographed (silica) to obtain tert-butyl-N-{5-[(9-fluoro-4,5-dihydrobenzo[2,3]-thiepino[4,5-d][1,3]thiazol-2-yl)amino]pentyl}-carbamate as a light tan solid.

5

General Procedure for the Deprotection of BOC-Protected Amines:

tert-butyl N-{[4-(4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}carbamate or
10 tert-butyl N-[6-(4,5-dihydrobenzo[2,3]-thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]carbamate were separately dissolved in Et₂O. The same volume of 4N HCl in dioxane was added to make a 2N solution. The reaction mixture was
15 stirred at room temperature overnight, and the solvent removed under reduced pressure to obtain the desired product as its HCl salt.

N1-(4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-yl)-1,4-butanediamine: 45% yield; ¹H NMR (CDCl₃) δ8.05 (dd, 1H, J= 0.56, 8.4 Hz), 7.33 (dd, 1H, J= 0.6, 8.4 Hz), 7.26 (t, 1H, J=6.5 Hz), 7.17 (t, 1H, J=6.5 Hz), 5.91 (broad, 1H), 3.20 (m, 6H), 2.69 (t, 2H, J=6.5 Hz), 1.61-1.27 (m, 6H).

25

N1-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-yl)-1,5-pentanediamine: 50% yield; ¹H NMR (CDCl₃) δ8.03 (dd, 1H, J= 0.6, 8.4 Hz), 7.49 (dd, 1H, J=0.6, 8.4 Hz), 7.28 (t, 1H, J=6.5 Hz), 7.16 (t, 1H, J=6.5 Hz), 5.92 (broad, 1H), 3.13 (m, 6H), 2.63 (t, 2H, J=6.5 Hz), 1.57-1.37 (m, 8H).

30

tert-Butyl N-{5-[(9-Fluoro-4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-

yl)amino]pentyl}carbamate: 60% yield; Anal. Calc. for $C_{21}H_{28}N_3F_2S_2O_2 + 0.15 CH_2Cl_2$: C, 56.41; H, 6.33; N, 9.3. Found : C, 56.45; H, 6.17; N, 8.9; 1H NMR ($CDCl_3$) δ 7.72 (dd, 1H, $J=1.15$, 7.5 Hz), 7.47-7.04 (m, 1H), 6.89-6.83 (m, 1H), 6.190-6.142 (m, 1H), 4.747-4.690 (m, 1H), 3.370-2.803 (m, 8H), 1.64-1.048 (m, 6H), 1.407 (s, 9H).

N2-[4-(Aminomethyl)cyclohexyl]-4,5-dihydrobenzo

[2,3]thiepino[4,5-d][1,3]thiazol-2-amine: 73% yield, 346 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.05 (dd, 1H, $J=1.2$, 7.9 Hz), 7.50 (dd, 1H, $J=1.2$, 7.7 Hz), 7.32 (apparent dt, 1H, $J=1.8$, 7.2 Hz), 7.15 (apparent dt, 1H, $J=1.7$, 7.2 Hz), 4.93 (b, 1H), 3.23 (m, 1H), 2.99 (t, 2H, $J=6.3$ Hz), 2.56 (d, 2H, $J=6.6$ Hz), 2.04 (ABM, 4H), 1.70-0.80 (m, 12H).

tert-Butyl N-[6-(4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]carbamate: 51% yield, 434 (ESMS, MH^+); 1H NMR (CD_3OD) δ 7.92 (d, 1H, $J=7.5$ Hz), 7.48 (d, 1H, $J=7.6$ Hz), 7.30 (apparent dt, 1H, $J=1.2$, 7.7 Hz), 7.15 (apparent dt, 1H, $J=1.5$, 7.5 Hz), 3.30 (t, 2H, $J=1.6$ Hz), 3.16 (t, 2H, $J=6.3$ Hz), 3.05 (t, 2H, $J=5.9$ Hz), 3.01 (t, 2H, $J=6.5$ Hz), 1.63 (m, 2H), 1.42 (s, 9H), 1.51-1.28 (m, 6H).

N1-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-yl)-1,6-hexanediamine: 75% yield, 334 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.05 (dd, 1H, $J=1.0$, 8.1 Hz), 7.51 (dd, 1H, $J=1.1$, 7.8 Hz), 7.32 (apparent dt, 1H, $J=1.4$, 7.4 Hz), 7.15, (apparent dt, 1H, $J=1.6$, 7.6 Hz), 5.15 (broad, 1H), 3.23 (m, 4H), 3.19 (s, 2H), 2.68 (t, 2H, $J=5.7$ Hz), 1.70-1.21 (m, 8H).

tert-Butyl N-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}carbamate: 44%

yield, 446 (ESMS, MH⁺); ¹H NMR (CD₃OD) δ 7.90 (dd, 1H, J= 1.2, 7.8 Hz), 7.49 (dd, 1H, J= 0.8, 7.8 Hz), 7.32 (apparent dt, 1H, J=1.4, 7.7 Hz), 7.16 (apparent dt, 1H, J=1.3, 7.6 Hz), 3.41 (m, 1H), 3.30 (m, 2H), 3.19 (t, 2H, J=6.5 Hz), 3.06, (t, 2H, J=5.8 Hz), 2.90 (d, 2H, J=7.0 Hz), 1.99 (ABm, 4H), 1.43 (s, 9H), 1.32-1.05 (m, 3H).

10 **General Procedure for the Derivatization of Amines with Carboxylic Acid and Sulfonic Acid Derivatives:**

An amine such as N1 -(4,5-dihydrobenzo-[2,3]thiepino[4,5-d] [1,3]thiazol-2-yl)-1,6-hexanediamine or N2-[4-(Aminomethyl)cyclohexyl]-4,5-dihydrobenzo[2,3]thiepino[4,5-d] [1,3]thiazol-2-amine (0.305 mmol) was dissolved in 2 ml CH₂Cl₂ containing 2 equivalents of diisopropylethylamine. A sulfonyl or acid chloride (1-3 equivalents) was added dropwise. The reaction mixture was stirred at room temperature for 1-3 days, quenched with water, washed with 10% NaHCO₃, dried over Na₂SO₄ and chromatographed using column chromatography or preparative TLC.

25 **General Procedure for the Derivatization of Tricyclic Amino Template such as N1-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d] [1,3]thiazol-2-yl)-1,6-hexanediamine Using Parallel Synthesis:**

30 Tricyclic amine templates such as N1-(4,5-dihydrobenzo[2,3]thiepino[4,5-d] [1,3]thiazol-2-yl)-1,6-hexanediamine (1 equivalent) or N2-[4-(aminomethyl)cyclohexyl]-4,5-dihydrobenzo[2,3]thiepino[4,5-d] [1,3]thiazol-2-amine (1 equivalent),

contained in a Robbins Scientific FlexChem 96-well assay, were treated with dichloromethane and poly(4-vinylpyridine). The required sulfonyl chloride, acid chloride, isocyanate or carbamyl chloride (1 equivalent) was added to each well. The reaction plates were rotated in a Robbins Scientific FlexChem rotating oven at room temperature for 24 hours, the contents filtered into a second reaction plate, and dichloromethane and polymer-supported tris(2-aminoethyl)amine were added. The second FlexChem plate was rotated at room temperature for an additional 24 hours. The contents were then filtered through a silica gel pad contained in a third Robbins plate and the filtrate collected in a 96-deep well plate. The wells were eluted with hexanes followed by EtOAc and a mixture of EtOAc : MeOH = 8 : 2. The solvent was removed and the crude products screened for affinity at hY5 (single point, 100 nM). Compounds exhibiting more than 50% inhibition were chromatographed for full pharmacological evaluation.

General Procedure for the Formation of Formamides:

tert-Butyl-*N*-[4-(Isopropylamino)cyclohexyl]methylcarbamate:

Isopropyl iodide (2 equivalents) was added dropwise to a suspension of *tert*-butyl *N*-[4-aminocyclohexyl]methylcarbamate (1 equivalent, [229 (ESMS, MH⁺): ¹H NMR (CD₃OD) δ 3.33 (m, 1H), 3.29 (m, 2H), 2.85 (d, 2H, J=6.4 Hz), 2.57 (m, 1H), 1.80 (ABm, 4H), 1.41 (s, 9H), 1.35 (m, 1H), 1.20-0.88 (m, 4H)]) and diisopropylethylamine (3 equivalents) in THF. The resulting mixture was stirred for 1 day. TLC analysis showed some starting amine. Isopropyl iodide (1 equivalent) and

diisopropylethyl amine (3 equivalents) were added to the reaction mixture which was then heated at 40 °C for 1 day. The reaction mixture was concentrated and chromatographed to give *tert*-butyl-*N*-[4-(isopropylamino)cyclohexyl]methyl carbamate: 22% yield, 271 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 4.65 (broad, 1H), 2.91 (m, 3H), 2.42 (m, 1H), 1.80 (ABm, 4H), 1.38 (s, 9H), 0.98 (d, 6H, $J=6.3$ Hz), 1.32-0.85 (m, 5H).

tert-Butyl-*N*-[4-(2-methoxyethylamino)-cyclohexyl]methylcarbamate was similarly obtained (2-methoxyethyl bromide and $n-Bu_4NI$ were used): 35% yield, 378 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 4.64 (broad, 1H), 3.44 (m, 2H), 3.31 & 3.30 (two s, 3H), 2.92 (m, 2H), 2.74 (m, 2H), 2.33 (m, 1H), 1.81 (ABm, 4H), 1.39 & 1.38 (two s, 9H), 1.34 (m, 1H), 0.98 (m, 4H).

tert-Butyl-*N*-[4-(isopropylformylamino)cyclohexyl]-methylcarbamate:

A solution of a *tert*-butyl *N*-[4-(isopropylamino)-cyclohexyl]methylcarbamate (7.89 mmol, 1 equivalent) in THF (5 ml) was added dropwise to a solution of 1*H*-benzotriazole-1-carboxaldehyde (8.68 mmol, 1.2 equivalent) in THF (10 ml) at room temperature, stirred overnight and heated at reflux temperature for two hours. 1*H*-Benzotriazole-1-carboxaldehyde (1 equivalent) was added and stirred overnight. The solvent was removed and dichloromethane was added to the residue. The organic extract was washed with 2*N* NaOH solution, washed with saturated NaCl solution, and dried over Na_2SO_4 . The solvent was then removed and the product chromatographed to give *tert*-butyl *N*-[4-(isopropylformylamino)cyclohexyl]methylcarbamate: 100% yield, 299 (ESMS, MH^+); 1H NMR (CD_3OD) δ 8.22 & 8.18 (two

s, 1H), 4.63 (broad, 1H), 4.30 & 3.60 (two m, 1H), 3.76 (m, 1H), 2.99 (m, 2H), 1.44 (s, 9H), 1.27 (d, 3H, J=6.5 Hz), 1.21 (d, 3H, J=6.5 Hz), 1.91-0.82 (m, 9H).

5 *N*-[4-(2-Methoxyethylformylamino)-cyclohexyl]

methylcarbamate was similarly prepared: 58% yield; 315 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.25 & 8.16 (two s, 1H), 4.80 (broad, 1H), 4.07 & 3.23 (two m, 1H), 3.50 (m, 2H), 3.40-3.33 (m, 2H), 3.31 (s, 3H), 2.99 (m, 2H), 1.46 (s, 9H), 1.86-0.95 (m, 9H).

N-[4-(Aminomethyl)cyclohexyl]-*N*-isopropylformamide:

15 Dioxane containing HCl was added (10 ml of 4N HCl solution) to the solution of *tert*-Butyl *N*-[4-(isopropylformylamino)cyclohexyl]methylcarbamate dissolved in 10 ml Et₂O, stirred at room temperature for 2 hours, and the solvent removed to obtain *N*-[4-(aminomethyl)cyclohexyl]-*N*-isopropylformamide: 100% yield, 20 199 (ESMS, MH⁺); ¹H NMR (CD₃OD) δ 8.16 (s, 1H), 4.16 & 3.57 (two m, 1H), 3.70 (m, 1H), 2.79 (m, 2H), 1.36 (m, 6H), 1.91-1.06 (m, 9H).

N-[4-(Aminomethyl)cyclohexyl]-*N*-(2-

25 methoxyethylformamide was similarly obtained: 100% yield; 215 (ESMS, MH⁺); ¹H NMR (CD₃OD) δ 8.44 & 8.03 4.65 (two s, 1H), 3.79-3.36 (m, 7H), 3.71 (s, 3H), 2.12-1.13 (m, 9H).

N-Benzoyl-*N'*-[4-(isopropylformylamino)cyclohexyl]-methylthiourea:

30

N-[4-(Aminomethyl)cyclohexyl]-*N*-isopropylformamide hydrochloride salt (4.55 mmol, 1 equivalent, obtained from previous step) was stirred at room temperature with benzoyl isothiocyanate (5.46 mmol, 1.2 equivalents) and

triethylamine (5.46 mmol, 1.2 equivalents) in THF (50 ml) overnight. Removal of the solvent followed by chromatography afforded a

5 light tan solid: 39% yield, 362 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 10.87 (broad, 1H), 9.20 (broad, 1H), 8.20 & 8.18 (two s, 1H), 7.83 (d, 2H, $J=7.7$ Hz), 7.60 (m, 1H), 7.49 (m, 2H), 4.26 (m, 1H), 3.76 & 3.08 (two m, 1H), 3.57 (m, 2H), 1.25 (d, 3H, $J=6.8$ Hz), 1.19 (d, 3H, $J=6.8$ Hz), 1.97-1.03 (m, 9H).

N-Benzoyl-*N'*-[4-(2-methoxyethylformyl-amino)cyclohexyl]methylthiourea was similarly obtained: 100% yield, 378 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 10.85 (broad, 1H), 9.03 (broad, 1H), 8.18 & 8.08 (two s, 1H), 7.84 (d, 2H, $J=7.9$ Hz), 7.64 (m, 1H), 7.52 (d, 2H, $J=7.8$ Hz), 3.63-3.24 (m, 7H), 3.34 & 3.33 (two m, 3H), 2.03-1.13 (m, 9H).

N-[4-(Isopropylformylamino)cyclohexyl]methylthiourea: 20 K_2CO_3 (2 equivalent) was dissolved in 20 ml of water and added to a solution of *N*-benzoyl-*N'*-[4-(isopropylformylamino)cyclohexyl]methylthiourea (obtained from the previous step) in MeOH, and the mixture stirred at room temperature overnight. The solvent was removed in 25 vacuo and the residue was dissolved in EtOH. The solution was filtered to remove a white precipitate and the filtrate was concentrated to afford a crude product which was chromatographed to yield the desired material: 100% yield; 258 (ESMS, MH^+); 1H NMR (CD_3OD) δ 8.15 & 8.13 (two s, 1H), 4.15 & 3.73 (two m, 1H), 3.34 & 2.97 (two m, 1H), 3.29 (m, 2H), 1.26 (d, 3H, $J=6.7$ Hz), 1.23 (d, 3H, $J=6.7$ Hz), 1.91-1.03 (m, 9H).

N-[4-(2-Methoxyethylformylamino)-cyclohexyl]methylthiourea was similarly prepared: 77% yield, 274 (ESMS, MH^+); 1H NMR (CD_3OD) δ 8.15 & 8.00 (two s, 1H), 7.55 & 7.43 (two m, 1H), 3.90 & 2.97 (two m, 1H), 3.46-3.28 (m, 10H), 1.90-0.99 (m, 9H).

N-4-[(4,5-Dihydrobenzo[2,3]thiepino[4,5-*d*][1,3]-thiazol-2-ylamino)methyl]cyclohexyl-*N*-isopropyl-formamide

N-[4-(Isopropylformylamino)cyclohexyl]methylthiourea

(obtained from the previous step) (0.029 mmol, 1 equivalent) and 4-bromo-2,3,4,5-tetrahydro-1-benzothiepin-5-one (0.044 mmol, 1.5 equivalent) were mixed with 2 equivalents diisopropylethyl amine in 10 ml of EtOH. The resulting mixture was heated at reflux temperature for 2 days. The resulting mixture was concentrated and the crude product was chromatographed (silica) to obtain the desired product. This procedure was used to prepare examples 163-166.

The following examples were prepared according to the reaction sequence of Schemes 11, 12 and 13 which describe the syntheses of sulfonamides, amides and ureas:

Example 103

N-[6-(4,5-Dihydrobenzo[2,3]thiepino[4,5-*d*][1,3]thiazol-2-ylamino)hexyl]methanesulfonamide: 74% yield, 413 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.02 (d, 1H, J = 7.9 Hz), 7.52 (d, 1H, J = 7.8 Hz), 7.33 (apparent t, 1H, J = 7.1 Hz), 7.16 (apparent t, 1H, J = 6.6 Hz), 5.24 (broad, 1H), 4.38 (broad, 1H), 3.20 (s, 2H), 4.15-3.09 (m, 4H), 2.95, (s, 2H), 1.63 (m, 6H), 1.41 (m, 4H).

Example 104

N-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}-methanesulfonamide: 81% yield,
5 424 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.03 (dd, 1H, J=0.7, 7.6 Hz), 7.52 (dd, 1H, J=0.8, 7.6 Hz), 7.33 (apparent dt, 1H, J=0.5, 7.6 Hz), 7.16 (apparent dt, 1H, J=1.3, 7.6 Hz), 4.32 (m, 1H), 3.27 (m, 1H), 3.19 (s, 2H), 3.01 (t, 2H, J=6.5 Hz), 2.96 (s, 3H), 2.08 (ABm, 4H), 1.75-1.46 (m, 10
4H), 1.32-1.05 (m, 3H).

Example 105

N1-[6-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]-1-ethanesulfonamide: 68% yield, 427 (ESMS, MH⁺);
15 ¹H NMR (CDCl₃) δ 8.05 (dd, 1H, J= 1.0, 8.4 Hz), 7.53 (dd, 1H, J=0.9, 7.6 Hz), 7.33 (apparent dt, 1H, J=1.3, 7.6 Hz), 7.16 (apparent dt, 1H, J=1.3, 7.6 Hz), 5.06 (m, 1H), 4.05 (m, 1H), 3.26 (m, 2H), 3.20 (s, 2H), 3.11 (m, 2H),
20 3.03 (q, 2H, J=7.5 Hz), 1.37 (t, 3H, J=7.5 Hz), 1.73-1.32 (m, 10H).

Example 106

N1-[6-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]-1-ethanesulfonamide: 87% yield; 480 (ESMS, MH⁺);
25 ¹H NMR (CDCl₃) δ 8.01 (dd, 1H, J=1.6, 7.6 Hz), 7.61-7.57 (m, 2H), 7.52 (dd, 1H, J=0.8, 7.4 Hz), 7.33 (apparent dt, 1H, J=1.5, 7.2 Hz), 7.15 (apparent dt, 1H, J=1.3, 7.2 Hz), 7.09 (dd, 1H, J=3.8, 4.8 Hz), 5.30 (broad, 1H), 4.78 (broad, 1H), 3.23 (broad m, 6H), 3.02 (broad m, 2H), 1.80-1.20 (m, 8H);
30 Anal. Calcd. For C₂₁H₂₅N₃O₂S₄+0.15CHCl₃: C, 51.05; H, 5.43; N, 8.50. Found: C, 51.05; H, 5.09; N, 8.44.

Example 107

N1-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}-1-ethanesulfonamide: 68%
yield, 438 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.05 (dd, 1H, $J=1.3$, 8.0 Hz), 7.52 (dd, 1H, $J=1.0$, 7.9 Hz), 7.33 (apparent dt, 1H, $J=1.3$, 7.6 Hz), 7.16 (apparent dt, 1H, $J=1.3$, 7.6 Hz), 4.89 (m, 1H), 4.20 (m, 1H), 3.29 (m, 1H), 3.19 (s, 2H), 3.05 (q, 2H, $J=7.5$ Hz), 2.99 (t, 2H, $J=6.4$ Hz), 2.09 (ABm, 4H), 1.53 (m, 2H), 1.38 (t, 3H, $J=7.5$ Hz), 1.17 (m, 5H).

Example 108

N2-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}-2-thiophenesulfonamide: 58%
yield; 492 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.00 (dd, 1H, $J=0.9$, 7.5 Hz), 7.62-7.59 (m, 2H), 7.52 (dd, 1H, $J=7.9$, 0.9 Hz), 7.32-7.09 (m, 3H), 5.01 (broad, 1H), 4.76 (broad, 1H), 3.23 (broad m, 5H), 2.88 (t, 2H, $J=6.6$ Hz), 2.00 (ABm, 4H), 1.70-0.80 (m, 6H); Anal. Calcd. For $C_{22}H_{25}N_3O_2S_4+0.5H_2O$: C, 52.77; H, 5.23; N, 8.39. Found: C, 53.02; H, 5.02; N, 8.26.

Example 109

N1-[5-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)pentyl]-1-ethanesulfonamide: 55% yield; Anal. Calc. for $C_{18}H_{26}N_4S_3O_2 + 0.7 CH_2Cl_2$: C, 47.68; H, 5.65; N, 8.92. Found: C, 47.89; H, 5.40; N, 8.83; 1H NMR ($CDCl_3$) δ 7.98 (dd, 1H, $J=0.6$, 7.5 Hz), 7.5 (dd, 1H, $J=0.6$, 7.5 Hz), 7.30 (t, 1H, $J=6.5$ Hz), 7.14 (t, 1H, $J=6.5$ Hz), 6.30 (broad, 1H), 5.50 (broad, 1H), 3.16 (s, 4H), 3.03-2.90 (m, 6H), 1.42-1.20 (m, 9H).

Example 110

N2-[5-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)pentyl]-2-thiophenesulfonamide: 50% yield; Anal. Calc. For $C_{20}H_{23}N_3S_3O_2 + 0.20 CH_2Cl_2$: C, 50.27; H, 4.89; N, 8.71. Found: C, 50.33; H, 4.84; N, 8.47; 1H NMR ($CDCl_3$) δ 7.86 (dd, 1H, J=0.6, 7.5 Hz), 7.60-7.50 (m, 2H), 7.47 (dd, 1H, J=0.6, 7.5 Hz), 7.26-7.04 (m, 3H) 6.22-6.14 (broad, 2H), 3.16 (m, 4H), 3.01 (t, 2H, J= 6.5 Hz), 2.83 (t, 2H, J=6.5 Hz), 1.45-1.11 (m, 6H).

Example 111

N4-[5-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)pentyl]-1-methyl-1H-4-imidazolesulfonamide: 45% yield; Anal. Calc. for $C_{20}H_{25}N_5S_3O_2 + 0.25 CH_2Cl_2$: C, 50.16; H, 5.30; N, 14.44. Found: C, 50.04; N, 5.24; H, 14.50; 1H NMR ($CDCl_3$) δ 7.10 (dd, 1H, J=0.6, 7.5 Hz), 7.72 (s, 1H), 7.66 (s, 1H), 7.44 (dd, 1H, J=0.6, 7.5 Hz), 7.31 (m, 1H), 7.147 (t, 1H, J=6.5 Hz), 3.311 (apparent s, 4H), 3.153-3.140 (m, 2H), 3.09 (s, 3H), 2.75 (t, 2H, J=4.5 Hz), 1.48-1.25 (m, 6H).

Example 112

N4-[6-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]-2,1,3-benzothiadiaazole-4-sulfonamide: 69% yield; 532 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.26 (m, 2H), 8.03 (dd, 1H, J=1.5, 7.5 Hz), 7.73 (dd, 1H, J=6.9, 8.7 Hz), 7.52 (dd, 1H, J=1.5, 7.2 Hz), 7.31 (apparent dt, 1H, J=1.5, 7.2 Hz), 7.15 (apparent dt, 1H, J=1.5, 7.2 Hz), 5.37 (broad, 1H), 5.03 (broad, 1H), 3.33 (m, 6H), 2.92 (apparent q, 2H, J=6.0 Hz), 1.70-1.20 (m, 8H); Anal.

Calcd. For $C_{23}H_{25}N_5O_2S_4+0.5H_2O$: C, 51.09; H, 4.85; N, 12.95.
Found: C, 51.09; H, 4.62; H, 12.68.

Example 113

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N1-[6-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]-2-methoxy-5-methyl-1-benzenesulfonamide:
74% yield; 518 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.04 (dd, 1H, $J=1.6, 8.2$ Hz), 7.71 (d, 1H, $J=1.8$ Hz), 7.52 (dd, 1H, $J=1.1, 7.8$ Hz), 7.35-7.23 (m, 2H), 7.16 (apparent dt, 1H, $J=7.2, 1.2$ Hz), 6.91 (d, 1H, $J=8.4$ Hz), 5.08 (broad t, 1H, $J=4.7$ Hz), 4.88 (t, 1H, $J=6.3$ Hz), 3.93 (s, 3H), 3.23 (m, 6H), 2.86 (apparent q, 2H, $J=6.6$ Hz), 2.33 (s, 3H), 1.70-1.20 (m, 8H); Anal. Calcd. For $C_{25}H_{31}N_3O_3N_3+0.5H_2O$: C, 57.01;
15 H, 6.12; N, 7.98. Found: C, 56.56; H, 5.85; N, 7.56.

Example 114

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N1-[6-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]-1-naphthalenesulfonamide: 83% yield; 524 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.65 (d, 1H, $J=9.2$ Hz), 8.26 (dd, 1H, $J=1.0, 7.0$ Hz), 8.07 (d, 1H, $J=8.2$ Hz), 8.02 (dd, 1H, $J=1.2, 7.7$ Hz), 7.97-7.50 (d, 4H), 7.28 (apparent dt, 1H, $J=1.3, 7.2$ Hz), 7.14 (apparent dt, 1H, $J=1.5, 7.2$ Hz),
25 5.13 (broad, 1H), 4.78 (broad, 1H), 3.12 (apparent q, 6H, $J=6.0$ Hz), 2.89 (apparent q, 2H, $J=6.6$ Hz), 1.70-1.20 (m, 8H); Anal. Calcd. For $C_{27}H_{29}N_3O_2S_3+0.4CH_2Cl_2$: C, 61.50; H, 5.62; N, 7.97. Found: C, 61.42; H, 5.43; N, 7.64.

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Example 115

N1-[6-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]-5-(dimethylamino)-1-naphthalenesulfonamide:
81% yield; 567 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.64 (d, 1H,

J=8.9 Hz), 8.29 (d, 1H, J=8.4 Hz), 8.25 (dd, 1H, J=1.2, 7.4 Hz), 8.02 (dd, 1H, J=1.6, 7.6 Hz), 7.59-7.12 (m, 6H), 3.12 (m, 6H), 2.86 (m, partially covered by singlet, 2H), 2.89 (s, 6H), 1.70-1.20 (m, 8H); Anal. Calcd. For $C_{29}H_{34}N_4O_2S_3$: C, 61.45; H, 6.05; N, 9.88. Found: C, 61.38; H, 6.00; N, 9.50.

Example 116

10 N1-[6-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]-2-nitro-1-benzenesulfonamide: 84% yield; 519 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.15-8.12 (m, 1H), 8.04 (dd, 1H, J=1.6, 8.0 Hz), 7.87-7.84 (m, 1H), 7.74-7.71 (m, 2H), 7.33 (apparent dt, 1H, J=1.3, 7.2 Hz), 7.16 (apparent
15 dt, 1H, J=1.2, 7.2 Hz), 5.30 (broad, 1H), 5.05 (broad, 1H), 3.23 (broad m, 6H), 3.12 (apparent q, 2H, J=6.6 Hz), 1.70-1.20 (m, 8H); Anal. Calcd. For $C_{23}H_{26}N_4O_4S_3+0.5H_2O$: C, 52.35; H, 5.16; N, 10.62. Found: C, 52.18; H, 4.85; N, 10.14.

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Example 117

N5-[6-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]-6-chloroimidazo[2,1-b][1,3]thiazole-5-sulfonamide: 68% yield; 554 (ESMS, MH^+); 1H NMR ($CDCl_3$)
25 δ 8.01 (dd, 1H, J=1.1, 7.6 Hz), 7.93 (d, 1H, J=4.6 Hz), 7.52 (dd, 1H, J=1.3, 7.6 Hz), 7.31 (apparent dt, 1H, J=1.2, 7.2 Hz), 7.15 (apparent dt, 1H, J=1.2, 7.2 Hz), 7.03 (d, 1H, J=4.6 Hz), 5.22 (broad, 2H), 3.23 (broad m, 6H), 3.02 (t, 2H, J=6.6 Hz), 1.70-1.20 (m, 8H); Anal.
30 Calcd. For $C_{24}H_{24}ClN_5O_2S_4+0.5H_2O$: C, 46.92; H, 4.47; N, 12.44. Found: C, 47.10; H, 4.25; N, 12.18.

Example 118

N4-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}-2,1,3-benzothiadiaazole-4-sulfonamide: 59% yield; 544 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.29-8.24 (m, 2H), 8.03 (dd, 1H, J=1.5, 7.9 Hz), 7.75 (dd, 1H, J=7.0, 8.8 Hz), 7.51 (dd, 1H, J=1.1, 7.8 Hz), 7.32 (apparent dt, 1H, J=1.2, 7.2 Hz), 7.15 (apparent dt, 1H, J=1.2, 7.2 Hz), 5.45 (t, 1H, J=6.9 Hz), 4.87 (broad d, 1H, J=8.1 Hz), 3.23 (broad m, 6H), 2.76 (t, 2H, J=5.7 Hz), 2.01 (ABm, 4H), 1.70-0.80 (m, 5H); Anal. Calcd. For C₂₄H₂₅N₅O₂S₂+0.5H₂O: C, 52.15; H, 4.74; N, 12.67. Found: C, 52.52; H, 4.59; N, 12.36.

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Example 119

N1-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}-2-methoxy-5-methyl-1-benzenesulfonamide: 58% yield; 530 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.03 (dd, 1H, J=1.6, 7.6 Hz), 7.71 (d, 1H, J=1.6 Hz), 7.51 (dd, 1H, J=1.2, 7.8 Hz), 7.35-7.25 (m, 2H), 7.16 (apparent dt, 1H, J=1.2, 7.2 Hz), 6.93 (d, 1, J=8.5 Hz), 5.95 (t, 1H, J=7.2 Hz), 4.86 (d, 1H, J=8.4 Hz), 3.95 (s, 3H), 3.23 (broad m, 5H), 2.71 (t, 2H, J=6.9 Hz), 2.35 (s, 3H), 2.02 (ABm, 4H), 1.70-0.80 (m, 5H); Anal. Calcd. For C₂₆H₃₁N₃O₃S₃+0.35CHCl₃: C, 55.38; H, 5.53; N, 7.35. Found: C, 55.15; H, 5.41; N, 7.13.

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Example 120

N2-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}-5-(2-pyridyl)-2-thiophenesulfonamide: 56% yield; 569 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.60 (dd, 1H, J=5.5 Hz), 8.00 (dd, 1H, J=1.6, 6.6

Hz), 7.80-7.25 (m, 7H), 7.15 (apparent dt, 1H, J=1.2, 7.2 Hz), 5.00 (broad m, 1H), 4.81 (broad m, 1H), 3.23 (broad m, 5H), 2.93 (m, 2H), 2.00 (ABm, 4H), 1.70-0.80 (m, 5H); Anal. Calcd. For $C_{27}H_{28}N_4O_2S_4$: C, 57.01; H, 4.96; N, 9.85. Found: C, 56.60; H, 4.78; N, 9.49.

Example 121

N1-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}-1-naphthalenesulfonamide: 58% yield; 536 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.65 (d, 1H, J=8.9 Hz), 7.25 (dd, 1H, J=7.3, 0.9 Hz), 8.10 (d, 1H, J=8.2 Hz), 7.98 (apparent dt, 2H, J=0.9, 6.5 Hz), 7.69-7.25 (m, 5H), 7.15 (apparent dt, 1H, J=1.2, 7.2 Hz), 5.00-4.80 (broad, 2H), 3.23 (broad m, 5H), 2.74 (t, 2H, J=6.9 Hz), 2.20-0.80 (m, 9H); Anal. Calcd. For $C_{28}H_{29}N_3O_2S_3+0.5H_2O$: C, 61.74; H, 5.55; N, 7.71. Found: C, 61.59; H, 5.19; N, 7.47.

Example 122

N1-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}-5-(dimethylamino)-1-naphthalenesulfonamide: 66% yield; 579 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.56 (d, 1H, J=8.1 Hz), 8.28 (d, 1H, J=8.9 Hz), 8.24 (dd, 1H, J=7.5, 0.9 Hz), 8.01 (dd, 1H, J=8.0, 0.9 Hz), 7.60-7.49 (m, 3H), 7.32-7.10 (m, 3H), 4.87 (d, 1H, J=6.6 Hz), 4.75 (t, 1H, J=5.4 Hz), 3.23 (broad m, 5H), 2.89 (s, 6H), 2.73 (t, 2H, J=6.6 Hz), 1.87 (ABm, 4H), 1.20-0.80 (m, 5H); Anal. Calcd. For $C_{30}H_{34}N_4O_2S_3+0.5H_2O$: C, 61.30; H, 6.00; N, 9.53. Found: C, 61.16; H, 5.76; N, 9.18.

Example 123

5 N1-[5-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)pentyl]-5-(dimethylamino)-1
naphthalenesulfonamide: 45% yield; Anal. Calc. for
C₂₈H₃₂N₄S₃O₂ + 0.3 CH₃COOC₂H₅: C, 60.55; H, 5.99; N, 9.67.
Found: C, 60.60; H, 5.86; N, 9.33; ¹H NMR (CDCl₃) δ 8.54
10 (dd, 1H, J=0.6, 7.5 Hz), 8.34 (dd, 1H, J=0.6, 7.5 Hz),
8.22 (dd, 1H, J=0.6, 7.5 Hz), 7.98 (dd, 1H, J=0.6, 7.5
Hz), 7.57-7.49 (m, 3H), 7.26-7.06 (m, 3H), 7.92 (broad,
1H), 5.66 (broad, 1H), 3.13 (apparent s, 4H), 2.94-2.82
(m, 2H), 2.87 (s, 6H), 2.83-2.76 (m, 2H), 1.31-1.04 (m,
15 6H).

Example 124

N1-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-
20 2-ylamino)cyclohexyl]methyl}-2-nitro-1-benzenesulfonamide:
54% yield; 531 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.15-8.12 (m,
1H), 8.04 (dd, 1H, J=0.9, 7.1 Hz), 7.89-7.76 (m, 2H), 7.76
(dd, 1H, J=0.9, 7.2 Hz), 7.32 (apparent dt, 1H, J=1.2, 7.2
Hz), 7.15 (apparent dt, 1H, J=1.2, 7.2 Hz), 5.36 (broad m,
25 1H), 4.86 (broad m, 1H), 3.25 (broad m, 5H), 2.96 (t, 2H,
J=6.6 Hz), 2.03 (ABm, 4H), 1.70-0.80 (m, 5H); Anal. Calcd.
For C₂₄H₂₆N₄O₄S₃+0.5H₂O: C, 53.41; H, 5.04; N, 10.38. Found:
C, 53.63; H, 4.72; N, 10.91.

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Example 125

N4-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-
2-ylamino)cyclohexyl]methyl}-1-methyl-1h-4-
imidazolesulfonamide: 28% yield; 490 (ESMS, MH⁺).

Example 126

5 N2-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}-5-(3-isoxazolyl)-2-thiophenesulfonamide: 94% yield; 559 (ESMS, MH^+); 1H NMR (CDCl₃) δ 8.32 (d, 1H, J=1.8 Hz), 7.98 (dd, 1H, J=8.1, 1.5 Hz), 7.59 (d, 1H, J=3.9 Hz), 7.50 (dd, 1H, J=1.6, 7.8 Hz), 7.46 (d, 1H, J=3.9 Hz), 7.31 (apparent dt, 1H, J=1.2, 7.2 Hz), 7.15 (apparent dt, 1H, J=1.2, 7.2 Hz), 6.53 (d, 1H, J=1.8 Hz), 5.01 (broad, 2H), 3.23 (broad m, 5H), 2.92 (broad m, 2H), 2.02 (ABm, 4H), 1.70-0.80 (m, 5H); Anal. Calcd. For C₂₅H₂₆N₄O₃S₄: C, 53.74; H, 4.69; N, 10.03. Found: C, 53.51; H, 4.56; N, 9.56.

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Example 127

N1-[5-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)pentyl]-1-naphthalene-sulfonamide: 45% yield; Anal. Calc. for C₂₆H₂₇N₃S₃O₂ + 0.2 CH₃COOC₂H₅: C, 61.04; H, 5.47; N, 9.97. Found: C, 61.35; H, 5.64; N, 7.67; 1H NMR (CDCl₃) δ 8.67 (dd, 1H, J=0.6, 7.5 Hz), 8.26 (dd, 1H, J=0.6, 7.5 Hz), 8.05 (dd, 1H, J=0.6, 7.5 Hz), 8.00-7.93 (m, 2H), 7.69-7.48 (m, 4H) 7.19-7.09 (m, 2H), 5.54-5.52 (m, 1H), 5.34-5.29 (m, 1H), 3.18 (apparent s, 4H), 3.02-2.96 (m, 2H), 2.81-2.82 (m, 2H), 1.39-1.08 (m, 6H).

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Example 128

30 N1-[5-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)pentyl]-2-fluoro-1-benzenesulfonamide: 45% yield; Anal. Calc. for C₂₂H₂₄FN₃S₃O₂ + 0.3 CH₃COOC₂H₅: C, 55.28; H, 5.28; N, 8.3. Found: C, 55.43; H, 5.25; N, 8.0. 1H NMR (CDCl₃) δ 7.97 (dd, 1H, J=0.6, 7.5 Hz), 7.84 (t, 1H, J=6.5

Hz), 7.58-7.48 (m, 2H), 7.27-7.09 (m, 4H), 6.09-6.08 (m, 1H), 5.69-5.60 (m, 1H), 3.16 (apparent s, 4H), 3.02 (t, 2H, J=6.5 Hz), 2.85 (t, 2H, J=6.5 Hz), 1.45-1.10 (m, 6H).

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Example 129

N2-[6-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]-5-(3-isoxazolyl)-2-thiophenesulfonamide:

59% yield; 547 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.31 (d, 1H, J=1.9 Hz), 7.98 (dd, 1H, J=1.6, 8.3 Hz), 7.57 (d, 1H, J=4.2 Hz), 7.51 (dd, 1H, J=1.3, 7.8 Hz), 7.44 (d, 1H, J=3.4 Hz), 7.28 (apparent dt, 1H, J=1.2, 7.2 Hz), 7.15 (apparent dt, 1H, J=1.2, 7.2 Hz), 6.51 (d, 1H, J=1.9 Hz), 5.33 (broad, 1H), 5.13 (broad, 1H), 3.23 (broad m, 6H), 3.03 (t, 2H, J=6.6 Hz), 1.80-1.20 (m, 8H); Anal. Calcd. For C₂₄H₂₆N₄O₃S₄+1.0H₂O: C, 51.04; H, 5.00; N, 9.92. Found: C, 50.80; H, 4.69; N, 9.45.

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Example 130

N1-[5-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)pentyl]-2-nitro-1-benzenesulfonamide: 40% yield; ¹H NMR (CDCl₃) δ 8.35-8.25 (m, 1H), 8.05 (d, 1H, J=7.5 Hz), 7.90-7.80 (m, 1H), 7.75-7.70 (m, 1H), 7.55 (d, 1H, J=7.5 Hz), 7.45-7.15 (m, 3H), 5.35-5.25 (m, 1H), 5.10-4.95 (broad, 1H), 3.25-3.10 (m, 6H), 2.40-2.30 (m, 2H), 1.80-1.25 (m, 6H).

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Example 131

N1-[5-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)pentyl]-2,6-dichloro-1-benzenesulfonamide: 40% yield; ¹H NMR (CDCl₃) δ 8.10-8.05 (m, 1H), 8.00 (d, 1H, J=7.5 Hz), 7.50 (d, 1H J=7.5 Hz), 7.48-7.42 (m, 1H), 7.35-

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7.25 (m, 3H), 5.05 (broad, 1H), 4.1 (broad, 1H), 3.28-3.18 (m, 6H), 3.00-2.90 (m, 2H), 1.75-1.25 (m, 6H).

Example 132

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N1-[5-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)pentyl]-2-bromo-6-methoxy-1-benzenesulfonamide:

35% yield; ¹H NMR (CDCl₃), δ 8.05-7.95 (m, 1H), 7.90-7.85 (m, 1H), 7.65-7.60 (m, 1H), 7.55-7.45 (m, 1H), 7.35-7.18 (m, 2H), 6.90-6.85 (m, 1H), 5.25-5.20 (m, 1H), 4.9 (broad, 1H), 3.95-3.90 (s, 3H), 3.30-3.18 (m, 6H), 2.95-2.85 (m, 2H), 1.75-1.18 (m, 6H).

Example 133

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N-[5-(4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)pentyl]phenyl-methanesulfonamide: 40% yield; ¹H NMR (CDCl₃), δ 8.05-7.95 (m, 2H), 7.65-7.50 (m, 2H), 7.4 (s, 5H), 5.30 (broad, 1H), 4.25 (broad, 1H), 3.30-3.15 (m, 6H), 3.05-2.95 (m, 2H), 2.35-2.25 (m, 2H), 1.80-1.25 (m, 6H).

Example 134

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N1-[5-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)pentyl]-2-fluoro-6-methyl-1-benzenesulfonamide:

30% yield; ¹H NMR (CDCl₃) δ 8.00 (d, 1H, J=7.5 Hz), 7.72-7.65 (m, 2H), 7.52 (d, 1H, J=7.5 Hz), 7.35-7.15 (m, 3H), 5.30 (broad, 1H), 4.65-4.55 (m, 1H), 3.25-3.18 (m, 6H), 3.00-2.90 (m, 2H), 2.60 (s, 3H), 1.82-1.25 (m, 6H).

Example 135

N1-[4-(4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)butyl]-2-fluoro-6-methyl-1-benzenesulfonamide: 35%
5 yield; ¹H NMR (CDCl₃) δ 8.00 (d, 1H, J=7.5 Hz), 7.72-7.65 (m, 2H), 7.52 (d, 1H, J=7.5 Hz), 7.35-7.15 (m, 3H), 5.30 (broad, 1H), 4.85-4.74 (m, 1H), 3.25-3.18 (m, 6H), 3.05-2.95 (m, 2H), 2.6 (s, 3H), 1.82-1.25 (m, 4H).

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Example 136

N1-[5-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)pentyl]-1-propanesulfonamide: 30% yield; ¹H NMR
(CDCl₃) δ 8.0 (d, 1H, J=7.5 Hz), 7.5 (d, 1H, J=7.5 Hz),
15 7.35-7.15 (m, 2H), 3.30-3.22 (m, 6H), 3.15-3.00 (m, 2H), 2.40-2.30 (m, 2H), 1.85-1.20 (m, 6H), 1.10-1.05 (m, 2H), 0.90-0.80 (m, 3H).

Example 137

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N1-[5-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)pentyl]-2,4-difluoro-1-benzenesulfonamide: 35%
yield; ¹H NMR (CDCl₃) δ 8.00 (d, 1H, J=7.5 Hz), 7.95-7.85 (m, 1H), 7.50 (d, 1H, J=7.5 Hz), 7.35-7.15 (m, 2H), 6.95-
25 7.05 (m, 2H), 4.82-4.75 (m, 1H), 4.80-4.75 (broad, 1H), 3.28-3.20 (m, 6H), 3.18-3.00 (m, 2H), 1.80-1.20 (m, 6H),

Example 138

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N1-[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)butyl]-2,4-difluoro-1-benzenesulfonamide: 35%
yield; ¹H NMR (CDCl₃) δ 8.00 (d, 1H, J=7.5 Hz), 7.95-7.85 (m, 1H), 7.50 (d, 1H, J=7.5 Hz), 7.35-7.15 (m, 2H), 6.95-

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7.05 (m, 1H), 5.15-5.08 (m, 1H), 4.90-4.80 (broad, 1H),
3.30-3.20 (m, 6H), 3.20-3.00 (m, 2H), 1.80-1.20 (m, 4H).

Example 139

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N'-[5-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)pentyl]-N,N-dimethylurea: 30% yield; ¹H NMR (CDCl₃), δ 8.05 (d, 1H, J=7.5 Hz), 7.5 (d, 1H, J=7.5 Hz), 7.42-7.15 (m, 2H), 5.48-5.35 (m, 1H), 4.5-4.4 (broad, 1H),
10 3.35-3.20 (m, 6H), 2.90 (s, 6H), 1.85-1.18 (m, 6H).

Example 140

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N1-[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)butyl]-1-naphthamide: 40% yield; ¹H NMR (CDCl₃), δ 8.32-8.25 (m, 1H), 8.05 (d, 1H, J=7.5 Hz), 7.92-7.85 (m, 2H), 7.60-7.40 (m, 4H), 7.32-7.25 (m, 2H), 7.18-7.10 (m, 1H), 6.20-6.10 (m, 1H), 5.40-5.30 (m, 1H), 3.65-3.55 (m, 2H), 3.40-3.30 (m, 2H), 3.20-3.15 (m, 4H), 1.80-1.18 (m, 4H).
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Example 141

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N2-[5-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)pentyl]-2-thiophenecarboxamide: 35% yield; ¹H NMR (CDCl₃) δ 8.05 (d, 1H, J=7.5 Hz), 7.55-7.45 (m, 3H), 7.35-7.28 (m, 1H), 7.20-7.12 (m, 1H), 7.10-7.05 (m, 1H), 6.08-6.02 (m, 1H), 5.30-5.20 (m, 1H), 3.50-3.40 (m, 2H), 3.31-3.22 (m, 1H), 3.20-3.15 (m, 4H), 1.80-1.12 (m, 6H).
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Example 142

N2-[5-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)pentyl]-2-naphthamide: 30% yield; ¹HNMR (CDCl₃), δ

8.15 (s, 1H), 8.10 (d, 1H, J=7.5 Hz), 7.95-7.80 (m, 4H),
7.60-7.55 (m, 3H), 7.25-7.22 (m, 1H), 7.18-7.08 (m, 1H),
6.20-6.15 (m, 1H), 5.15-5.10 (m, 1H), 3.55-3.45 (m, 2H),
3.35-3.22 (m, 2H), 3.20-3.15 (m, 4H), 2.20-1.25 (m, 6H).

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Example 143

N1-[6-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]-1-propanesulfonamide: 10% yield, 440 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.05 (dd, 1H, J=1.6, 8.0 Hz), 7.51

(dd, 1H, J=1.4, 7.9 Hz), 7.33 (apparent dt, 1H, J=1.6, 7.5 Hz), 7.16 (apparent dt, 1H, J=1.4, 8.0 Hz), 5.03 (m, 1H),
4.15 (m, 1H), 3.27 (m, 2H), 3.20 (m, 2H), 3.11 (q, 2H, J=7.1 Hz), 2.98 (t, 2H, J=8.0 Hz), 1.84 (q, 2H, J=7.7),
1.69-1.40 (m, 10H), 1.26 (t, 3H, J=7.1 Hz).

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Example 144

N1-[6-(4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]-3-(trifluoromethyl)-1-benzenesulfonamide:

18% yield, 542 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.13 (s, 1H),
8.05 (d, 1H, J=8.0 Hz), 8.00 (dd, 1H, J=1.7, 8.0 Hz), 7.84 (dd, 1H, J=0.8, 7.1 Hz), 7.67 (apparent dt, 1H, J=0.5, 8.0 Hz), 7.52 (dd, 1H, J=1.2, 7.5 Hz), 7.30 (apparent dt, 1H, J=1.0, 7.6 Hz), 7.15 (apparent dt, 1H, J=1.2, 7.5 Hz),
5.23 (m, 1H), 4.75 (m, 1H), 3.21 (m, 2H), 3.20 (s, 2H),
2.96 (m, 2H), 1.75-1.28 (m, 10H).

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Example 145

N1-[6-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]-2,4-difluoro-1-benzenesulfonamide: 14%
5 yield, 510 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.03 (dd, 1H, $J=1.6, 7.7$ Hz), 7.92 (apparent q, 1H, $J=7.7$ Hz), 7.52 (dd, 1H, $J=1.2, 6.6$ Hz), 7.30 (apparent dt, 1H, $J=1.6, 7.6$ Hz), 7.16 (apparent dt, 1H, $J=1.5, 7.6$ Hz), 6.99 (m, 2H), 5.07 (m, 1H), 4.72 (m, 1H), 3.23 (m, 2H), 3.20 (s, 1H), 2.98
10 (m, 2H), 1.62-1.28 (m, 10H).

Example 146

N1-[6-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]-2,6-dichloro-1-benzenesulfonamide: 6%
15 yield, 542 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.09 (m, 1H), 8.03 (dm, 1H, $J=8.5$ Hz), 7.52 (dm, 1H, $J=7.7$ Hz), 7.47 (m, 2H), 7.36-7.3 (m, 1H), 7.15 (tm, 1H, $J=7.2$ Hz), 4.98 (b, 1H), 3.30-3.20 (m, 3H), 2.95 (apparent q, 2H, $J=7.4$ Hz),
20 1.70-1.20 (m, 12H).

Example 147

N1-[6-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]-2-bromo-6-methoxy-1-benzenesulfonamide:
25 20% yield, 582 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.06-8.03 (m, 2H), 7.62 (dd, 1H, $J=2.6, 8.9$ Hz), 7.54-7.47 (m, 1H), 7.23 (apparent dt, 1H, $J=1.2, 7.2$ Hz), 7.15 (apparent dt, 1H, $J=1.2, 7.2$ Hz), 6.91 (d, 1H, $J=9.2$ Hz), 4.95 (b, 1H), 4.83
30 (t, 1H, $J=6.6$ Hz), 3.95 (s, 3H), 3.23 (m, 2H), 2.90 (apparent q, 2H, $J=6.8$ Hz), 1.70-1.20 (m, 9H).

Example 148

N-[6-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]phenylmethane-sulfonamide: 8% yield, 488 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.05 (dd, 1H, $J=1.1$, 7.8 Hz), 7.48 (dd, 1H, $J=1.1$, 7.2 Hz), 7.39 (m, 5H), 7.23 (apparent dt, 1H, $J=1.2$, 7.2 Hz), 7.15 (apparent dt, 1H, $J=1.2$, 7.2 Hz), 4.98 (b, 1H), 4.55 (s, 2H), 4.03 (b, 1H), 3.25 (m, 2H), 2.97 (m, 2H), 1.70-1.20 (m, 8H).

Example 149

N1-[6-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)hexyl]-2-fluoro-6-methyl-1-benzenesulfonamide: 24% yield, 506 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.03 (dd, 1H, $J=1.5$, 8.0 Hz), 7.69 (dd, 1H, $J=2.8$, 8.7 Hz), 7.52 (dd, 1H, $J=1.3$, 7.6 Hz), 7.31 (m, 2H), 7.16 (m, 2H), 5.11 (m, 1H), 4.62 (m, 1H), 3.21 (m, 2H), 3.20 (s, 2H), 2.95 (m, 2H), 2.60 (s, 3H), 1.59-1.25 (m, 10H).

Example 150

N1-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}-3-(trifluoromethyl)-1-benzenesulfonamide: 12% yield, 554 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.13 (s, 1H), 8.06 (dd, 1H, $J=1.0$, 7.2 Hz), 8.00 (dd, 1H, $J=0.7$, 7.3 Hz), 7.86 (dd, 1H, $J=1.0$, 8.0 Hz), 7.69 (t, 1H, $J=7.8$ Hz), 7.51 (dd, 1H, $J=1.0$, 7.6 Hz), 7.30 (t, 1H, $J=8.0$ Hz), 7.15 (apparent dt, 1H, $J=1.0$, 7.2 Hz), 4.99 (m, 1H), 4.62 (m, 1H), 3.24 (m, 2H), 3.19 (s, 2H), 2.86 (t, 2H, $J=6.4$ Hz), 2.00 (ABm, 4H), 1.63-1.03 (m, 6H).

Example 151

N1-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}-2,4-difluoro-1-benzenesulfonamide: 16% yield, 522 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.03 (dd, 1H, J=1.0, 8.0 Hz), 7.9 (m, 1H), 7.51 (dd, 1H, J=1.0, 7.7 Hz), 7.32 (apparent dt, 1H, J=1.2, 7.6 Hz), 7.16 (apparent dt, 1H, J=1.3, 7.6 Hz), 7.00 (m, 1H), 4.88 (m, 1H), 4.75 (m, 1H), 3.25 (m, 1H), 3.19 (s, 2H), 2.85 (t, 2H, J=6.5 Hz), 2.05 (ABm, 4H), 1.60-1.45 (m, 4H), 1.26-1.04 (m, 3H).

Example 152

N1-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}-2,6-dichloro-1-benzenesulfonamide: 18% yield, 554 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.09 (d, 1H, J=1.0, Hz), 8.0 (m, 1H), 7.53-7.48 (m, 3H), 7.32 (apparent dt, 1H, J=0.9, 7.5 Hz), 7.15 (apparent dt, 1H, J=1.5, 7.5 Hz), 5.09 (m, 1H), 4.90 (m, 1H), 3.23 (m, 1H), 3.19 (s, 2H), 2.79 (t, 1H, J=6.4 Hz), 2.04 (ABm, 4H), 1.61 (m, 2H), 1.45 (m, 2H), 1.27-1.03 (m, 3H).

Example 153

N-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}phenyl-methanesulfonamide: 4% yield, 500 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.03 (dm, 1H, J=8.1 Hz), 7.51 (dm, 1H, J=8.1 Hz), 7.40 (s, 5H), 7.32 (tm, 1H, J=7.1 Hz), 7.16 (tm, 1H, J=7.1 Hz), 4.93 (b, 1H), 4.26 (s, 2H), 4.09 (b, 1H), 3.24 (b, 2H), 3.19 (s, 2H), 2.85 (t, 2H, J=6.7 Hz), 2.02 (ABm, 4H), 1.70-1.01 (m, 6H).

Example 154

5 N1-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-
2-ylamino)cyclohexyl]methyl}-2-cyano-1-benzenesulfonamide:
16% yield, 511 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.04 (dm, 1H,
J=7.8 Hz), 7.93-7.78 (m, 4H), 7.51 (dm, 1H, J=7.3 Hz),
7.35-7.15 (m, 2H), 4.95 (b, 1H), 4.10 (b, 1H), 3.66 (m,
2H), 3.33 (m, 2H), 2.40-1.20 (m, 12H).

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Example 155

15 N1-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-
2-ylamino)cyclohexyl]methyl}-4-fluoro-1-
benzenesulfonamide: 4% yield, 504 (ESMS, MH⁺); ¹H NMR
(CDCl₃) δ 8.02 (dm, 1H, J=8.7 Hz), 7.90-7.85 (m, 2H), 7.51
(dm, 1H, J=7.9 Hz), 7.36-7.16 (m, 4H), 4.86 (b, 1H), 4.42
(b, 1H), 3.30-3.20 (m, 2H), 2.83 (t, 2H, J=6.7 Hz), 2.02
(ABm, 4H), 1.70-0.80 (m, 12H).

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Example 156

25 N1-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-
2-ylamino)cyclohexyl]methyl}-4-methyl-1-
benzenesulfonamide: 10% yield, 500 (ESMS, MH⁺); ¹H NMR
(CDCl₃) δ 8.02 (dd, 1H, J= 1.5, 8.0 Hz), 7.41 (d, 1H, J=7.6
Hz), 7.51 (d, 1H, J=7.0 Hz), 7.33-7.28 (m, 3H), 7.15
(apparent dt, 1H, J=1.2, 7.7 Hz), 4.92 (m, 1H), 4.39 (m,
1H), 3.24 (m, 1H), 3.19 (s, 2H), 2.80 (t, 2H, J=6.7 Hz),
30 2.44 (s, 3H), 2.02 (ABm, 4H), 1.60-1.01 (m, 7H).

Example 157

35 N8-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-
2-ylamino)cyclohexyl]methyl}-8-quinolinesulfonamide: 53%

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yield, 537 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 9.04 (dd, 1H, $J=1.6, 4.2$), 8.45 (dd, 1H, $J=1.6, 7.4$ Hz), 8.31 (dd, 1H, $J=1.8, 8.3$ Hz), 8.08 (dd, 1H, $J=1.3, 8.2$ Hz), 8.02 (dd, 1H, $J=1.4, 7.9$ Hz), 7.68 (t, 1H, $J=7.7$ Hz), 7.59 (dd, 1H, $J=4.1, 8.2$ Hz), 7.51 (dd, 1H, $J=1.3, 7.7$ Hz), 7.31 (apparent dt, 1H, $J=1.5, 7.6$ Hz), 7.15 (apparent dt, 1H, $J=1.5, 7.3$ Hz), 6.41 (t, 1H, $J=6.1$ Hz), 4.89 (broad, 1H), 4.15 (broad, 1H), 3.23 (broad, 1H), 3.18 (s, 2H), 2.71 (t, 2H, $J=6.6$ Hz), 2.35 (t, 2H, $J=7.5$ Hz), 1.99 (ABm, 4H), 1.74-0.86 (m, 5H).

Example 158

N1-{[4-(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)cyclohexyl]methyl}-2-fluoro-6-methyl-1-benzenesulfonamide: 10% yield, 518 (ESMS, MH^+); 1H NMR ($CDCl_3$) δ 8.04 (d, 1H, $J=7.2$ Hz), 7.54 (d, 1H, $J=5.2$ Hz), 7.37-7.26 (m, 4H), 7.16 (tm, 1H, $J=7.0$ Hz), 4.94 (broad, 1H), 4.59 (broad, 1H), 3.26 (m, 1H), 3.19 (s, 2H), 3.01 (m, 2H), 2.05 (ABM, 4H), 1.45 (s, 3H), 1.63-0.88 (m, 7H).

Example 159

N-{5-[(9-Fluoro-4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-yl)amino]pentyl}methanesulfonamide: 45% yield; Anal. Calc. for $C_{17}H_{22}N_3S_3O_2F$: C, 49.2; H, 5.34; N, 10.10. Found: C, 49.35; H, 5.33; N, 9.84; 1H NMR ($CDCl_3$) δ 7.77 (dd, 1H, $J=1.1, 7.5$ Hz), 7.47 (dd, 1H, $J=1.5, 7.5$ Hz), 6.87 (m, 1H), 5.46-5.41 (m, 1H), 4.77-4.71 (m, 1H), 3.30-3.00 (m, 8H), 2.96 (s, 3H), 1.76-1.20 (m, 6H).

Example 160

N1-{5-[(9-Fluoro-4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-yl)amino]pentyl}-2-methoxy-5-methyl-1-benzenesulfonamide: 55% yield; Anal. Calc. for $C_{24}H_{28}N_3FS_3O_3$: C, 55.26; H, 5.41; N, 8.05. Found: C, 55.18; H, 5.58; N, 7.82; 1H NMR ($CDCl_3$), δ 7.75 (dd, 1H, J=1.1, 7.5 Hz), 7.70 (s, 1H), 7.45 (m, 1H), 7.29 (dd, 1H, J=1.1, 7.5 Hz), 6.94-6.86 (m, 2H), 5.14-5.13 (m, 1H), 4.94-4.98 (m, 1H), 3.93 (s, 3H), 3.26-3.12 (m, 6H), 2.91-2.83 (m, 2H), 2.33 (s, 3H), 1.70-1.13 (m, 6H).

Example 161

N1-{5-[(9-Fluoro-4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-yl)amino]pentyl}-2-fluoro-1-benzenesulfonamide: 45% yield; Anal. Calc. for $C_{22}H_{23}N_3F_2S_3O_2$: C, 53.31; H, 4.68; N, 8.48. Found: C, 53.40; H, 4.87; N, 8.15; 1H NMR ($CDCl_3$) δ 7.92 (t, 1H, J=6.5 Hz), 7.74 (dd, 1H, J=1.1, 7.5 Hz), 7.60-7.53 (m, 1H), 7.47-7.46 (m, 1H), 7.30-7.18 (m, 2H), 6.89-6.83 (m, 1H), 5.43-5.40 (m, 1H), 5.16-5.12 (m, 1H), 3.24-3.12 (m, 6H), 2.99-2.92 (m, 2H), 1.59-1.29 (m, 6H).

Example 162

N2-{5-[(9-Fluoro-4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-yl)amino]pentyl}-2-thiophene-sulfonamide: 45% yield; Anal. Calc. for $C_{20}H_{22}N_3FS_4O_2$: C, 49.67; H, 4.58; N, 8.6. Found: C, 49.25; H, 4.67; N, 8.2; M^+ At 484. 1H NMR ($CDCl_3$), δ 7.74 (dd, 1H, J=1.1, 7.5 Hz), 7.59-7.54 (m, 2H), 7.49-7.44 (m, 1H), 7.09-7.01 (m, 1H), 6.88-6.83 (m, 1H), 5.47-5.44 (m, 1H), 5.06-5.02 (m, 1H), 3.26-3.12 (m, 6H), 3.02-2.96 (m, 2H), 1.60-1.15 (m, 6H).

The following examples were prepared according to Scheme 11b which describes the synthesis of formamides:

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Example 163

trans-N-4-[(4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)methyl]cyclohexyl-N-(2-methoxyethyl)formamide: 40% yield, 432 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.17 & 8.08 (two s, 1H), 8.01 (dm, 1H, J=8.0 Hz), 7.53 (dm, 1H, J=7.7 Hz), 7.34 (tm, 1H, J=7.5 Hz), 7.17 (dt, 1H, J=1.0, 8.0 Hz), 5.53 (b, 1H), 3.53-3.38 (m, 3H), 3.48 (s, 3H), 3.19 (s, 2H), 3.24-3.07 (m, 4H), 1.98-1.01 (m, 11H).

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Example 164

trans-N-(4-[(9-Fluoro-4,5-dihydrobenzo[2,3]thiepino-[4,5-d][1,3]thiazol-2-yl)amino]methylcyclohexyl)-N-(2-methoxyethyl)formamide: 24% yield, 450 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.18 & 8.08 (two s, 1H), 7.77 (m, 1H), 7.47 (m, 1H), 6.80 (m, 1H), 5.21 (m, 1H), 3.48 (s, 3H), 3.43 (m, 3H), 3.33 (s, 2H), 3.15 (m, 4H), 1.99-1.05 (m, 11H).

25

Example 165

trans-N-4-[(4,5-Dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-ylamino)methyl]cyclohexyl-N-isopropylformamide: 43% yield; 416 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.22 & 8.18 (two s, 1H), 8.03 (dd, 1H, J=1.4, 7.8 Hz), 7.52 (dd, 1H, J=1.5, 8.4 Hz), 7.33 (apparent t, 1H, J=7.0 Hz), 7.16 (apparent dt, 1H, J=1.5, 8.4 Hz), 5.62-5.31 (b, 1H), 3.19 (s, 2H), 3.16 (m, 2H), 3.08 (m,

30

3H), 1.94-1.54 (m, 7H), 1.23 & 1.20 (two s, 6H), 1.14-1.01 (m, 3H).

Example 166

5

N-(4-[(9-Fluoro-4,5-dihydrobenzo[2,3]thiepino[4,5-d][1,3]thiazol-2-yl)amino]methylcyclohexyl)-*N*-isopropylformamide: 62% yield, 434 (ESMS, MH⁺); ¹H NMR (CDCl₃) δ 8.21 & 8.18 (two s, 1H), 7.76 (dd, 1H, J=2.9, 10.7 Hz), 7.47 (m, 1H), 6.87 (m, 1H), 5.52 (m, 1H), 4.29 & 3.60 (two m, 1H), 3.88 (m, 1H), 3.22-3.06 (m, 6H), 1.27 (d, 3H, J=6.9 Hz), 1.21 (d, 3H, J=6.9 Hz), 1.92-0.90 (m, 9H).

15

II. Synthetic Methods for General Structures

A. Triazine Compounds

20

The examples described in Section IA are merely illustrative of the methods used to synthesize triazine derivatives. Further derivatives may be obtained utilizing methods shown in Schemes 1-5. The substituents in Schemes 1-5 are described in the Detailed Description as relates to triazine compounds.

25

30

It may be necessary to incorporate protection and deprotection strategies for substituents such as amino, amido, carboxylic acid, and hydroxyl groups in the synthetic methods described above to form triazine derivatives. Methods for protection and deprotection of such groups are well-known in the art, and may be found, for example in Green, T. W. and Wuts, P.G. M. (1991) Protection Groups in Organic Synthesis, 2nd Edition John Wiley & Sons, New York.

B. Bicyclic Compounds

The examples described in Section IB are merely illustrative of the methods used to synthesize bicyclic derivatives. Further derivatives may be obtained
5 utilizing methods shown in Schemes 6-10. The substituents in Schemes 6-10 are described in the Detailed Description as relates to bicyclic compounds.

It may be necessary to incorporate protection and
10 deprotection strategies for substituents such as amino, amido, carboxylic acid, and hydroxyl groups in the synthetic methods described above to form bicyclic derivatives. Methods for protection and deprotection of such groups are well-known in the art, and may be found,
15 for example in Green, T. W. and Wuts, P.G. M. (1991) Protection Groups in Organic Synthesis, 2nd Edition John Wiley & Sons, New York.

C. Tricyclic Compounds

20 The examples described in Section IC are merely illustrative of the methods used to synthesize tricyclic compounds. Further compounds may be obtained utilizing methods shown in Schemes 11-15. The substituents in Schemes 11-15 are described in the Detailed Description as
25 relates to tricyclic compounds.

It may be necessary to incorporate protection and
deprotection strategies for substituents such as amino,
30 amido, carboxylic acid, and hydroxyl groups in the synthetic methods described above to form tricyclic derivatives. Methods for protection and deprotection of such groups are well-known in the art, and may be found, for example in Green, T.W. and Wuts, P.G.M. (1991)

Protection Groups in Organic Synthesis, 2nd Edition John Wiley & Sons, New York.

5 III. Oral Compositions

As a specific embodiment of an oral composition of a compound of this invention, 100 mg of one of the compounds described herein is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

10

IV. Pharmacological Evaluation of Compounds at Cloned Neuropeptide Y-type Receptors

The pharmacological properties of the compounds of the present invention were evaluated at one or more of the cloned human neuropeptide Y-type receptors Y1, Y2, Y4, and Y5, using protocols described below.

15

Cell Culture

20 COS-7 cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 µg/ml streptomycin) at 37 °C, 5% CO₂. Stock plates of COS-7 cells were trypsinized and split 1:6 every 3-4 days. Human embryonic kidney 293 cells were grown on 25 150 mm plates in D-MEM with supplements (minimal essential medium) with Hanks' salts and supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 µg/ml streptomycin) at 37 °C, 5% CO₂. Stock plates of 293 cells were 30 trypsinized and split 1:6 every 3-4 days. Mouse fibroblast LM(tk-) cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/mL

penicillin/100 µg/mL streptomycin) at 37 °C, 5% CO₂. Stock plates of LM(tk-) cells were trypsinized and split 1:10 every 3-4 days.

5 LM(tk-) cells stably transfected with the human Y5 receptor were routinely converted from an adherent monolayer to a viable suspension. Adherent cells were harvested with trypsin at the point of confluence, resuspended in a minimal volume of complete DMEM for a
10 cell count, and further diluted to a concentration of 10⁶ cells/ml in suspension media (10% bovine calf serum, 10% 10X Medium 199 (Gibco), 9 mM NaHCO₃, 25 mM glucose, 2 mM L-glutamine, 100 units/ml penicillin/100 µg/ml streptomycin, and 0.05% methyl cellulose). The cell
15 suspension was maintained in a shaking incubator at 37 °C, 5% CO₂ for 24 hours. Membranes harvested from cells grown in this manner may be stored as large, uniform batches in liquid nitrogen. Alternatively, cells may be returned to adherent cell culture in complete DMEM by distribution
20 into 96-well microtiter plates coated with poly-D-lysine (0.01 mg/ml) followed by incubation at 37 °C, 5% CO₂ for 24 hours. Cells prepared in this manner yielded a robust and reliable NPY-dependent response in cAMP radio-immunoassays as further described hereinbelow.

25 Mouse embryonic fibroblast NIH-3T3 cells were grown on 150 mm plates in Dulbecco's Modified Eagle Medium (DMEM) with supplements (10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 µg/ml streptomycin) at 37 °C, 5%
30 CO₂. Stock plates of NIH-3T3 cells were trypsinized and split 1:15 every 3-4 days.

Sf9 and Sf21 cells were grown in monolayers on 150 mm tissue culture dishes in TMN-FH media supplemented with 10% fetal calf serum, at 27 °C, no CO₂. High Five insect cells were grown on 150 mm tissue culture dishes in Ex-Cell 400™ medium supplemented with L-Glutamine, also at 27 °C, no CO₂.

Transient Transfection

All receptor subtypes studied (human and rat Y1, human and rat Y2, human and rat Y4, human and rat Y5) were transiently transfected into COS-7 cells by the DEAE-dextran method, using 1 µg of DNA /10⁶ cells (Cullen, 1987). The human Y1 receptor was prepared using known methods (Larhammar, et al., 1992).

Stable Transfection

Human Y1, human Y2, and rat Y5 receptors were co-transfected with a G-418 resistant gene into the human embryonic kidney 293 cell line by a calcium phosphate transfection method (Cullen, 1987). Stably transfected cells were selected with G-418. Human Y4 and human Y5 receptors were similarly transfected into mouse fibroblast LM(tk-) cells and NIH-3T3 cells.

Binding of the compounds of the present invention to human Y1, Y2, Y4, and Y5 receptors was evaluated using stably transfected 293 or LM(tk-) cells as described above. Stably transfected cell lines which may be used for binding assays include, for example, for the human Y1 receptor, 293-hY1-5 (deposited June 4, 1996, under ATCC Accession No. CRL-12121), for the human Y2 receptor, 293-hY2-10 (deposited January 27, 1994, under ATCC Accession No. CRL-11537), for the human Y4 receptor, L-hY4-3 (deposited January 11, 1995, under ATCC Accession No. CRL-

11779), and for human Y5 receptor, L-hY5-7 (deposited November 15, 1995, under ATCC Accession No. CRL-11995). These cell lines were deposited with the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, Virginia 20110-2209, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure.

10 Membrane Harvest

Membranes were harvested from COS-7 cells 48 hours after transient transfection. Adherent cells were washed twice in ice-cold phosphate buffered saline (138 mM NaCl, 8.1 mM Na₂HPO₄, 2.5 mM KCl, 1.2 mM KH₂PO₄, 0.9 mM CaCl₂, 0.5 mM MgCl₂, pH 7.4) and lysed by sonication in ice-cold sonication buffer (20 mM Tris-HCl, 5 mM EDTA, pH 7.7). Large particles and debris were cleared by low speed centrifugation (200 x g, 5 min, 4 °C). Membranes were collected from the supernatant fraction by centrifugation (32,000 x g, 18 min, 4 °C), washed with ice-cold hypotonic buffer, and collected again by centrifugation (32,000 x g, 18 min, 4 °C). The final membrane pellet was resuspended by sonication into a small volume of ice-cold binding buffer (~1 ml for every 5 plates: 10 mM NaCl, 20 mM HEPES, 0.22 mM KH₂PO₄, 1.26 mM CaCl₂, 0.81 mM MgSO₄, pH 7.4). Protein concentration was measured by the Bradford method (Bradford, 1976) using Bio-Rad Reagent, with bovine serum albumin as a standard. Membranes were held on ice for up to one hour and used fresh, or flash-frozen and stored in liquid nitrogen.

Membranes were prepared similarly from 293, LM(tk-), and NIH-3T3 cells. To prepare membranes from baculovirus infected cells, 2 x 10⁷ Sf21 cells were grown in 150mm

tissue culture dishes and infected with a high-titer stock of hY5BB3. Cells were incubated for 2-4 days at 27 °C, no CO₂ before harvesting and membrane preparation as described above.

5

Membranes were prepared similarly from dissected rat hypothalamus. Frozen hypothalami were homogenized for 20 seconds in ice-cold sonication buffer with the narrow probe of a Virtishear homogenizer at 1000 rpm (Virtis, Gardiner, NY). Large particles and debris were cleared by centrifugation (200 x g, 5 min, 4 °C) and the supernatant fraction was reserved on ice. Membranes were further extracted from the pellet by repeating the homogenization and centrifugation procedure two more times. The supernatant fractions were pooled and subjected to high speed centrifugation (100,000 x g, 20 min. 4 °C). The final membrane pellet was resuspended by gentle homogenization into a small volume of ice-cold binding buffer (1 mL/gram wet weight tissue) and held on ice for up to one hour, or flash-frozen and stored in liquid nitrogen.

20

Radioligand Binding to Membrane Suspensions

25

Membrane suspensions were diluted in binding buffer supplemented with 0.1% bovine serum albumin to yield an optimal membrane protein concentration so that ¹²⁵I-PYY (or alternative radioligand such as ¹²⁵I-NPY, ¹²⁵I-PYY₃₋₃₆, or ¹²⁵I-[Leu³¹Pro³⁴]PYY) bound by membranes in the assay was less than 10% of ¹²⁵I-PYY (or alternative radioligand) delivered to the sample (100,000 dpm/sample = 0.08 nM for competition binding assays). ¹²⁵I-PYY (or alternative radioligand) and peptide competitors were also diluted to desired concentrations in supplemented binding buffer. Individual samples were then prepared in 96-well

30

polypropylene microtiter plates by mixing ^{125}I -PYY (25 μL) (or alternative radioligand), competing peptides or supplemented binding buffer (25 μL), and finally, membrane suspensions (200 μL). Samples were incubated in a 30 °C water bath with constant shaking for 120 min. Incubations were terminated by filtration over Whatman GF/C filters (pre-coated with 1% polyethyleneimine and air-dried before use), followed by washing with 5 mL of ice-cold binding buffer. Filter-trapped membranes were impregnated with MeltiLex solid scintillant (Wallac, Turku, Finland) and counted for ^{125}I in a Wallac Beta-Plate Reader. Alternatively, incubations were carried out in GF/C filter plates (pre-coated with 1% polyethyleneimine and air-dried before use), followed by vacuum filtration and three washes of 300 μL of ice-cold binding buffer. 50 μL of UltimaGold (Packard) scintillant were added and counted for ^{125}I in a Wallac MicroBeta Trilux. Non-specific binding was defined by 300 nM human NPY for all receptors except the Y4 subtypes; 100 nM human PP was used for the human Y4 and 100 nM rat PP for the rat Y4. Specific binding in time course and competition studies was typically 80%; most non-specific binding was associated with the filter. Binding data were analyzed using nonlinear regression and statistical techniques available in the GraphPAD Prism package (San Diego, CA).

Functional Assay: Radioimmunoassay of cAMP

Stably transfected cells were seeded into 96-well microtiter plates and cultured until confluent. To reduce the potential for receptor desensitization, the serum component of the media was reduced to 1.5% for 4 to 16 hours before the assay. Cells were washed in Hank's buffered saline, or HBS (150 mM NaCl, 20 mM HEPES, 1 mM CaCl_2 , 5 mM KCl, 1 mM MgCl_2 , and 10 mM glucose)

supplemented with 0.1% bovine serum albumin plus 5 mM theophylline and pre-equilibrated in the same solution for 20 min at 37 °C in 5% CO₂. Cells were then incubated 5 min with 10 µM forskolin and various concentrations of receptor-selective ligands. The assay was terminated by the removal of HBS and acidification of the cells with 100 mM HCl. Intracellular cAMP was extracted and quantified with a modified version of a magnetic bead-based radioimmunoassay (Advanced Magnetix, Cambridge, MA). The final antigen/antibody complex was separated from free ¹²⁵I-cAMP by vacuum filtration through a PVDF filter in a microtiter plate (Millipore, Bedford, MA). Filters were punched and counted for ¹²⁵I in a Packard gamma counter. Binding data were analyzed using nonlinear regression and statistical techniques available in the GraphPAD Prism package (San Diego, CA).

Functional Assay: Intracellular calcium mobilization

The intracellular free calcium concentration was measured by microspectrofluorometry using the fluorescent indicator dye Fura-2/AM. Stably transfected cells were seeded onto a 35 mm culture dish containing a glass coverslip insert. Cells were washed with HBS and loaded with 100 µl of Fura-2/AM (10 µM) for 20 to 40 min. After washing with HBS to remove the Fura-2/AM solution, cells were equilibrated in HBS for 10 to 20 min. Cells were then visualized under the 40X objective of a Leitz Fluovert FS microscope and fluorescence emission was determined at 510 nM with excitation wave lengths alternating between 340 nM and 380 nM. Raw fluorescence data were converted to calcium concentrations using standard calcium concentration curves and software analysis techniques.

Materials

Cell culture media and supplements were from Specialty Media (Lavallette, NJ). Cell culture plates (150 mm and 96-well microtiter) were from Corning (Corning, NY). Sf9, Sf21, and High Five insect cells, as well as the baculovirus transfer plasmid, pBlueBacIIITM, were purchased from Invitrogen (San Diego, CA). TMN-FH insect medium complemented with 10% fetal calf serum, and the baculovirus DNA, BaculoGoldTM, was obtained from Pharmingen (San Diego, CA.). Ex-Cell 400TM medium with L-Glutamine was purchased from JRH Scientific. Polypropylene 96-well microtiter plates were from Co-star (Cambridge, MA). All radioligands were from New England Nuclear (Boston, MA). Commercially available NPY and related peptide analogs were either from Bachem California (Torrance, CA) or Peninsula (Belmont, CA); [D-Trp³²]NPY and PP C-terminal fragments were synthesized by custom order from Chiron Mimotopes Peptide Systems (San Diego, CA). Bio-Rad Reagent was from Bio-Rad (Hercules, CA). Bovine serum albumin (ultra-fat free, A-7511) was from Sigma (St. Louis. MO). All other materials were reagent grade.

Radioligand Binding Assay Results

The compounds described above were assayed using cloned human NPY receptors. The preferred compounds were found to be selective NPY (Y5) antagonists. Example 49 has been assayed using the cloned human NPY receptors and a K_i (nM) > 100000 was determined for NPY (Y1), NPY (Y2), and NPY (Y4). The binding affinities of several compounds for NPY (Y5) are illustrated in Tables 1-6.

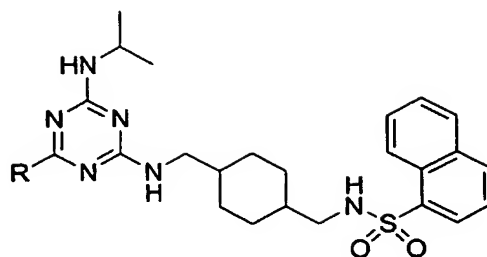
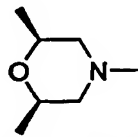
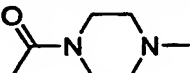
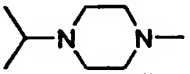


Table 1.

Example #	R	K _i (nM) hNPY-5
1	CH ₃ NH-	13
2	CH ₃ CH ₂ NH-	7
3	CH ₂ =CHCH ₂ NH-	12
4	(CH ₃) ₂ CHNH-	23
5	CH ₃ CH ₂ CH ₂ NH-	18
6	CH ₃ CH ₂ CH ₂ CH ₂ NH-	22
7		22
8		9
9	CH ₃ CH ₂ CH ₂ CH ₂ CH ₂ NH-	6
10	NCCH ₂ CH ₂ NH-	81
11	HOCH ₂ CH ₂ NH-	35
12	CH ₃ OCH ₂ CH ₂ NH-	18
13	CH ₃ OCH ₂ CH ₂ CH ₂ NH-	22
14	(CH ₃) ₂ NCH ₂ CH ₂ NH-	194
15		83
16		313
17	(CH ₃) ₂ N-	27
18	CH ₃ CH ₂ (CH ₃)N-	32
19	(CH ₃ CH ₂) ₂ N-	53
20		19
21		71
22		38
23		68
24		40

Table 1 (continued)

25		135
26	HOCH ₂ CH ₂ (CH ₃)N-	86
27		31
28		22

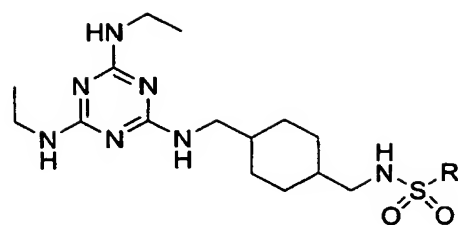
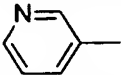
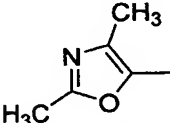
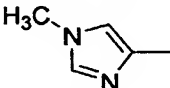
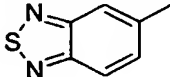
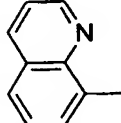


Table 2.

Example #	R	K _i (nM) hNPY-5
29	4-t-butylphenyl	50
30	4-fluorophenyl	40
31	2-methoxy-5-methylphenyl	25
32	2-fluorophenyl	35
33	2-methylphenyl	22
34		427
35	4-methoxyphenyl	82
36		71
37	thiophen-2-yl	55
38		313
39	4-methylphenyl	28
40		5
41		13
42	Methyl	3067

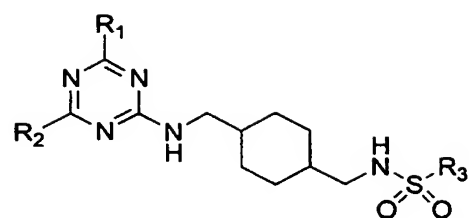
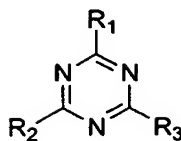


Table 3.

Example #	R ₁	R ₂	R ₃	K _i (nM) hNPY-5
43				43
44				295
45				59
46			4-t-butylphenyl	68
47				359
48				192
49		chloro	1-naphthyl	138
50				3508
51		chloro	4-t-butylphenyl	3544
52			4-fluorophenyl	101
53	chloro	chloro		20654
54			2-methoxy-5-methylphenyl	---
55		2-pyridyl	4-fluorophenyl	209



5

Table 4.

Example #	R_1	R_2	R_3	K_i (nM) hNPY-5
56				94406
57				>100000
58				>100000

Table 5

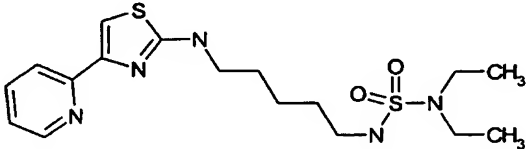
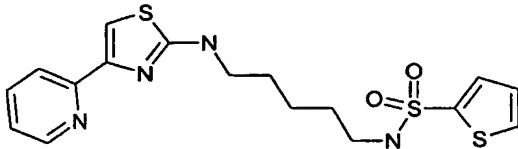
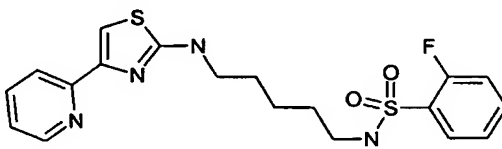
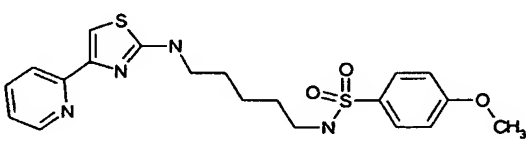
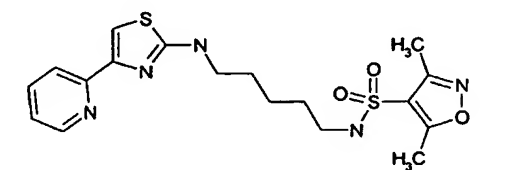
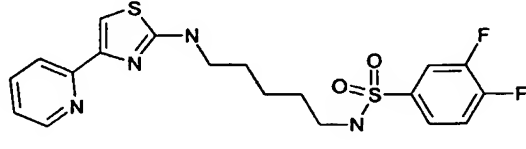
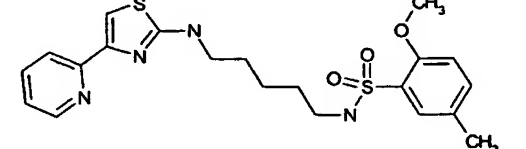
EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1, 2, 4
59		3.7	>10000
60		31	
61		9.7	>10000
62		33	
63		18.7	>10000
64		42	
65		2.7	>10000

Table 5 continued

5

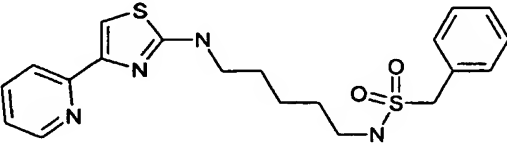
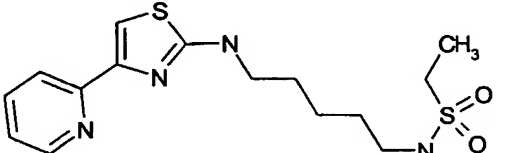
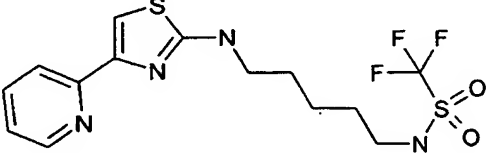
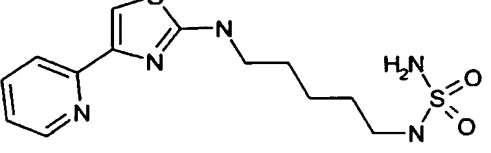
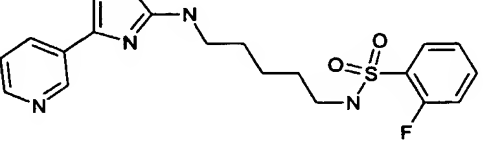
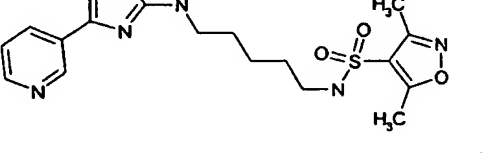

EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1, 2, 4
66		45	
67		150	
68		109	
69		804	
70		21	>10000
71		37	>10000
72		50	>10000

Table 5 continued

EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1,2,4
73		204	>10000
74		745	>10000
75		5	>10000
76		11	>10000
77		297	>10000
78		891	>10000
79		545	>10000

Table 5 continued

EXAMPLE No.	STRUCTURE	K_i , nM hNPY-5	K_i , nM hNPY-1,2,4
80		40	>10000
81		155	>10000
82		8.3	>10000
83		4	
84		8.4	
85		3.8	
86		12.3	

Table 5 continued

EXAMPLE No.	STRUCTURE	K_i , nM hNPY-5	K_i , nM hNPY-1,2,4
87		17	
88		13.7	
89		3.2	
90		17.5	
91		12.4	
92		7.9	
93		3.6	

Table 5 continued

EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1,2,4
94		19.5	
95		179	
96		8.1	
97		6.6	
98		1.5	
99		3.1	
100		3.3	

Table 5 continued

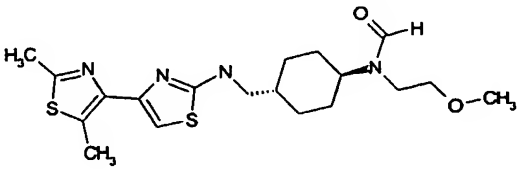
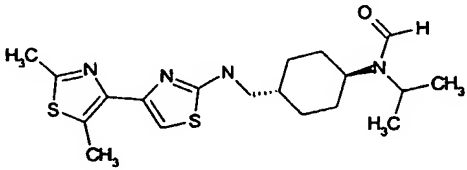
EXAMPLE No.	STRUCTURE	K_i , nM hNPY-5	K_i , nM hNPY-1,2,4
101		407	
102		72	

Table 6

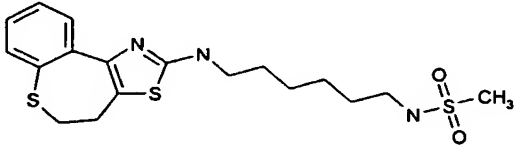
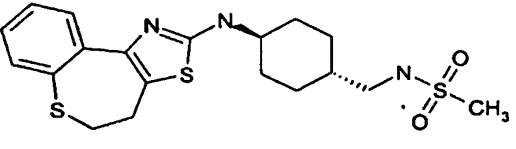
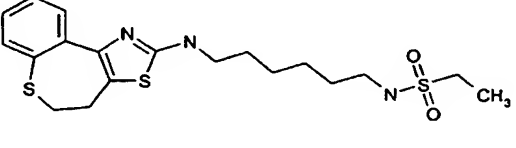
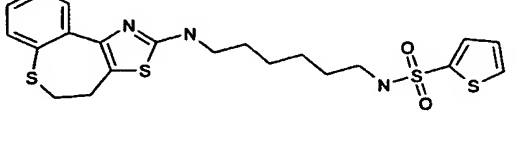
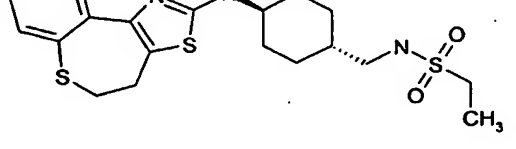
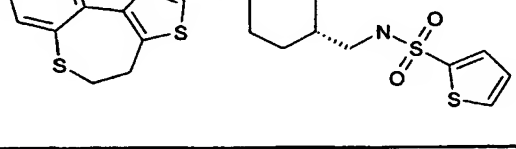
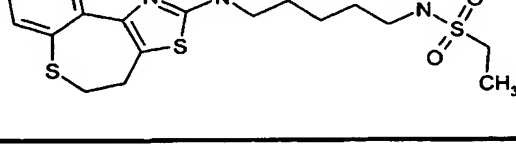
EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1,2,4
103		7.4	
104		6.8	
105		5.4	
106		2.9	>10000
107		5.1	>10000
108		5.1	
109		3.7	>10000

Table 6 continued

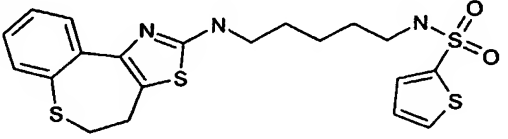
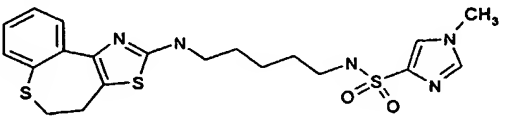
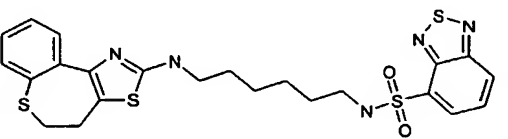
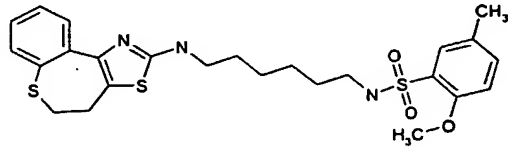
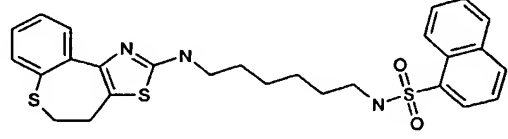
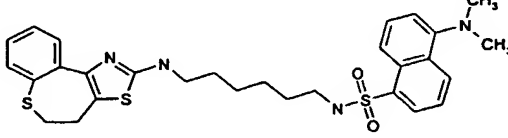
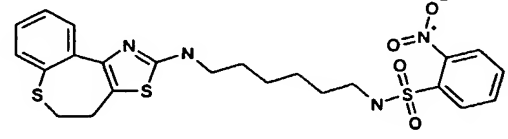
EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1,2,4
110		2.6	>10000
111		17.2	
112		4.4	
113		5.4	
114		16.6	
115		71	
116		7.1	

Table 6 continued

EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1, 2, 4
117		6.6	
118		2.4	>10000
119		14.1	
120		54	
121		18.4	
122		27	
123		161	

Table 6 continued

EXAMPLE	STRUCTURE	K_i , nM	K_i , nM
No.		hNPY-5	hNPY-1,2,4
124		11.5	
125		33	
126		34	
127		17.2	
128		3.7	
129		29	
130		5.2	

Table 6 continued

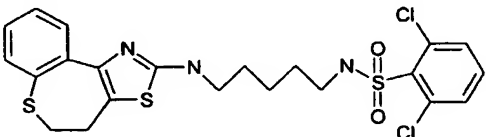
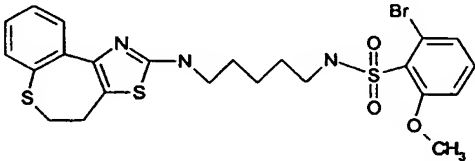
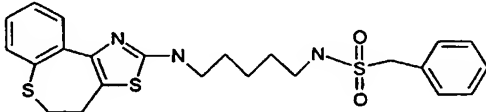
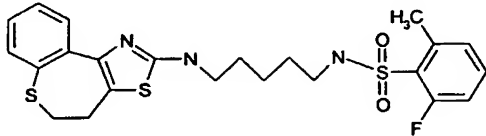
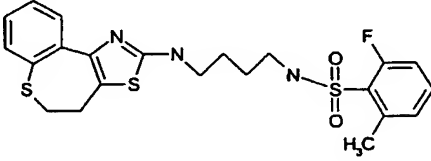
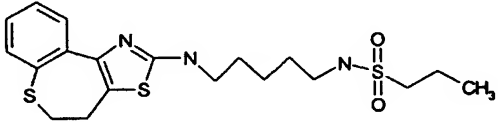
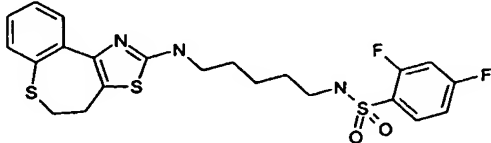
EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1,2,4
131		71	
132		9.7	
133		38	
134		8.3	
135		110	
136		24	
137		6.5	

Table 6 continued

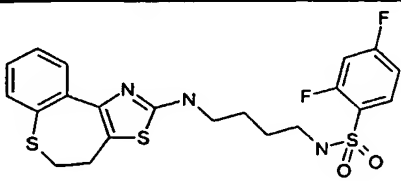
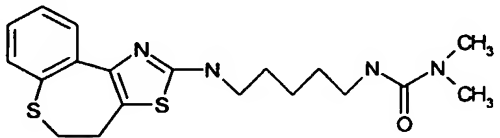
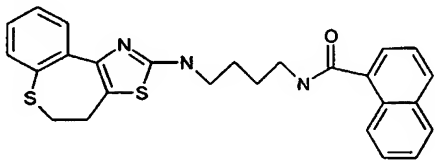
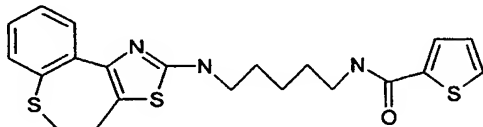
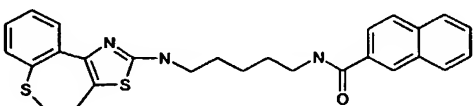
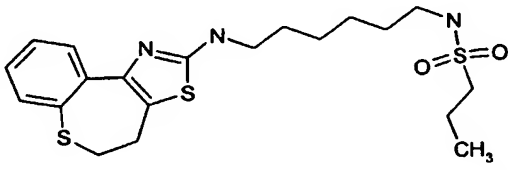
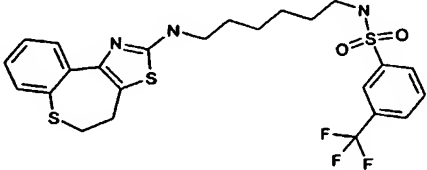
EXAMPLE No.	STRUCTURE	K_i , nM hNPY-5	K_i , nM hNPY-1,2,4
138		119	
139		122	
140		123	
141		84	
142		100	
143		3.6	
144		22.4	

Table 6 continued

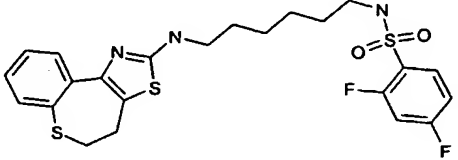
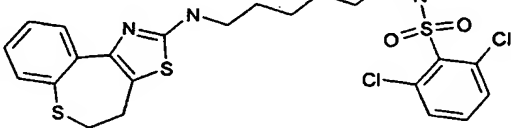
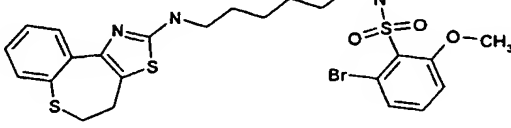
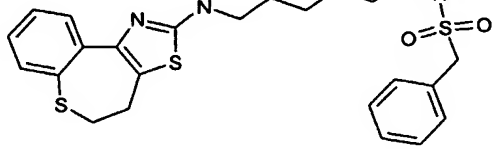
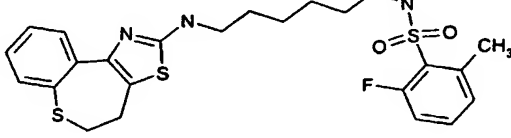
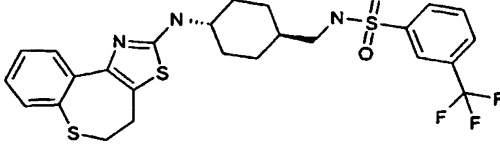
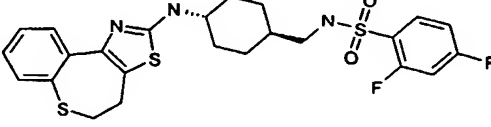
EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1,2,4
145		4.1	
146		25	
147		7.9	
148		10.5	
149		4	
150		21	
151		7.9	

Table 6 continued

EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1,2,4
152		17.4	
153		8.9	
154		69	
155		9.1	
156		6.6	
157		5.7	
158		8.2	>10000

Table 6 continued

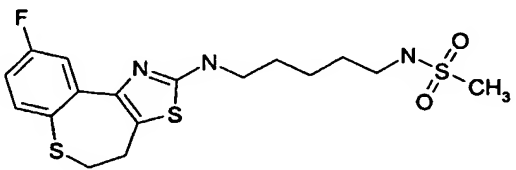
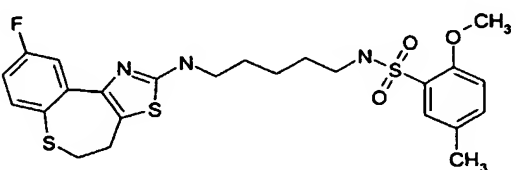
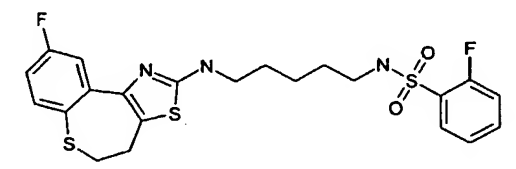
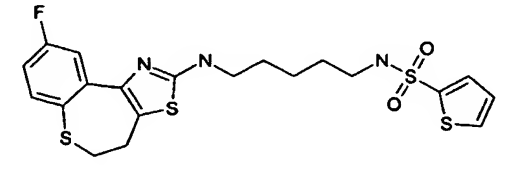
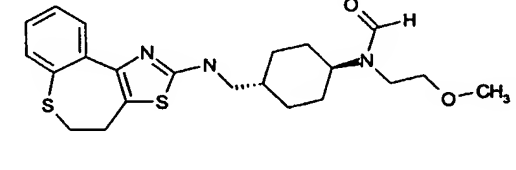
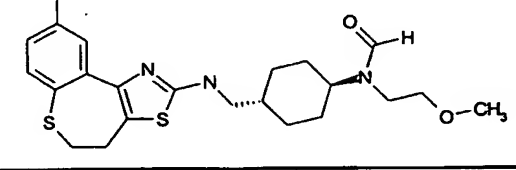
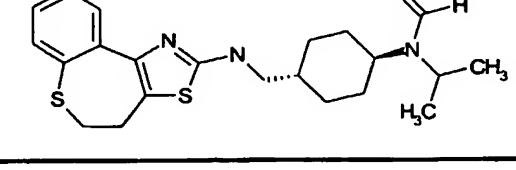
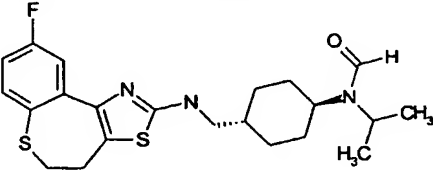
EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1,2,4
159		6.1	>10000
160		2.8	>10000
161		4.9	>10000
162		4.8	>10000
163		12.3	
164		13	
165		4.8	

Table 6 continued

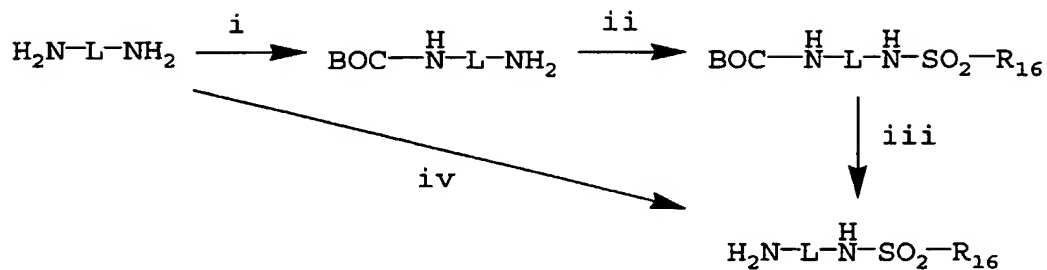
EXAMPLE No.	STRUCTURE	K _i , nM hNPY-5	K _i , nM hNPY-1,2,4
166		6	

Functional Assay Results

5 The functional in vitro activity of several compounds was characterized using a radioimmunoassay of cAMP, the results of which are summarized in Table 7.

10 Table 7. Functional Antagonism Data

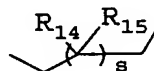
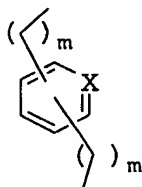
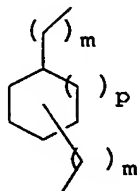
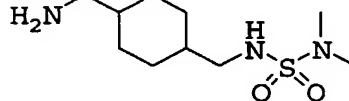
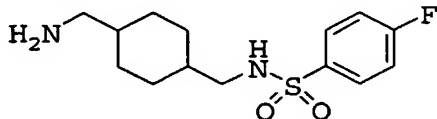
Example #	K _i (h NPY-5), nM	pK _b
1	13	6.7
37	55	6.8
49	138	6.0
65	2.7	7.8
98	1.5	8.4
104	6.8	8.6
157	5.7	7.7

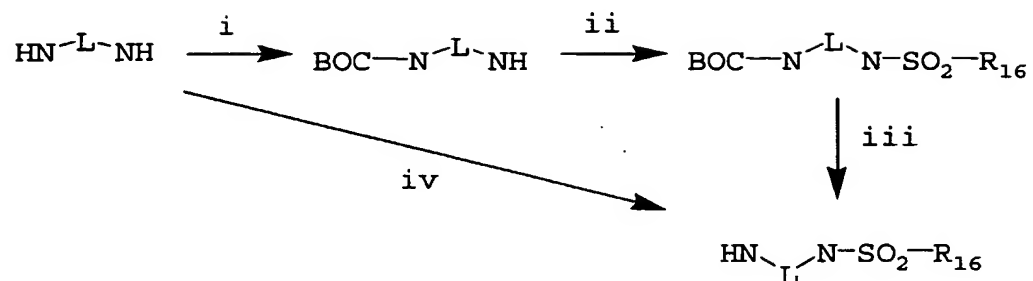
Schem 1A. Synthesis of Side Chains

i) BOC_2O , CH_2Cl_2 , DIEA; ii) $\text{R}_{16}\text{SO}_2\text{Cl}$, DIEA;
 iii) TFA, CH_2Cl_2 ; iv) $\text{R}_{16}\text{SO}_2\text{Cl}$, DIEA

R_{14} , R_{15} , R_{16} , X, m, p, and s are described herein

L =

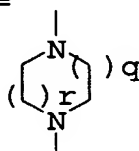
**Examples:**

Scheme 1B. Synthesis of Side Chains

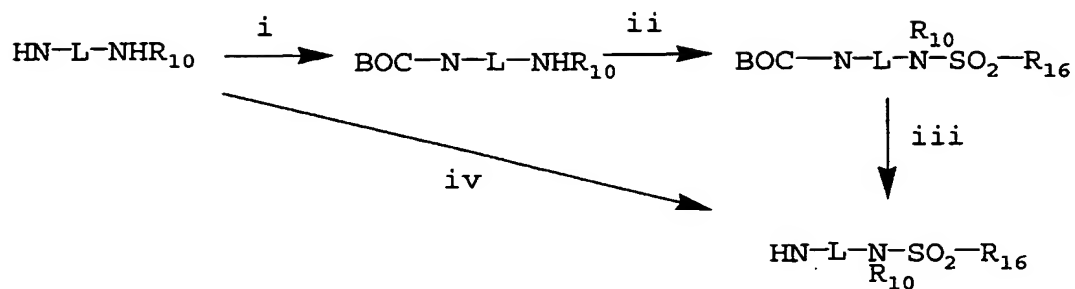
i) BOC_2O , CH_2Cl_2 , DIEA; ii) $\text{R}_{16}\text{SO}_2\text{Cl}$, DIEA;
 iii) TFA, CH_2Cl_2 ; iv) $\text{R}_{16}\text{SO}_2\text{Cl}$, DIEA

R_{16} , q, and r are described herein

N-L-N =



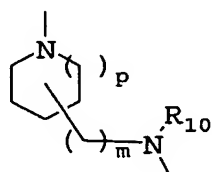
Scheme 1C. Synthesis of Side Chains

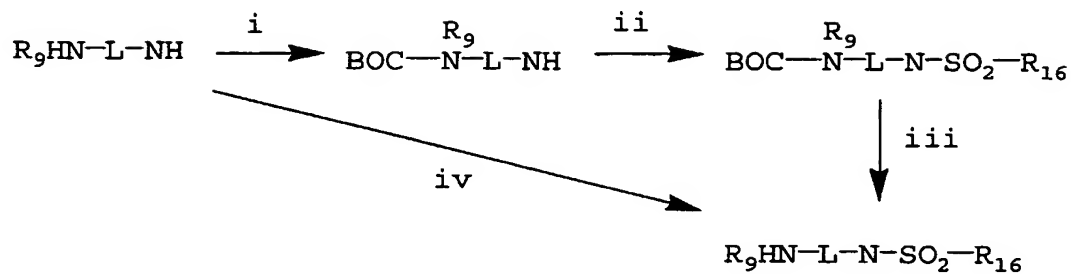


i) BOC_2O , CH_2Cl_2 , DIEA; ii) $\text{R}_{16}\text{SO}_2\text{Cl}$, DIEA;
 iii) TFA, CH_2Cl_2 ; iv) $\text{R}_{16}\text{SO}_2\text{Cl}$, DIEA

R_{16} , R_{10} , m, and p are described herein

$\text{N-L-NR}_{10} =$

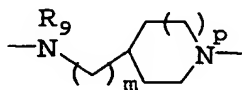


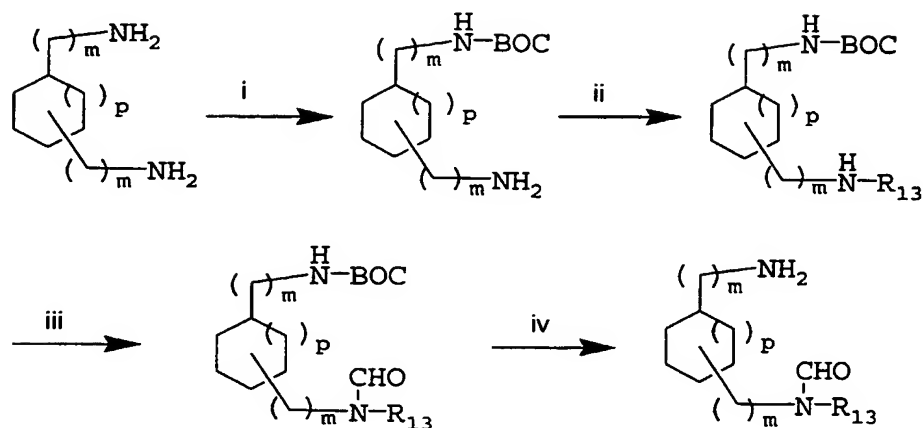
Schem 1D. Synthesis of Side Chains

i) BOC_2O , CH_2Cl_2 , DIEA; ii) $R_{16}SO_2Cl$, DIEA;
 iii) TFA, CH_2Cl_2 ; iv) $R_{16}SO_2Cl$, DIEA

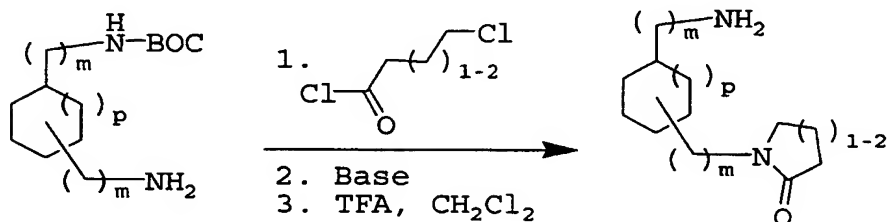
R_{16} , R_9 , p, and m are described herein

$R_9N-L-N =$



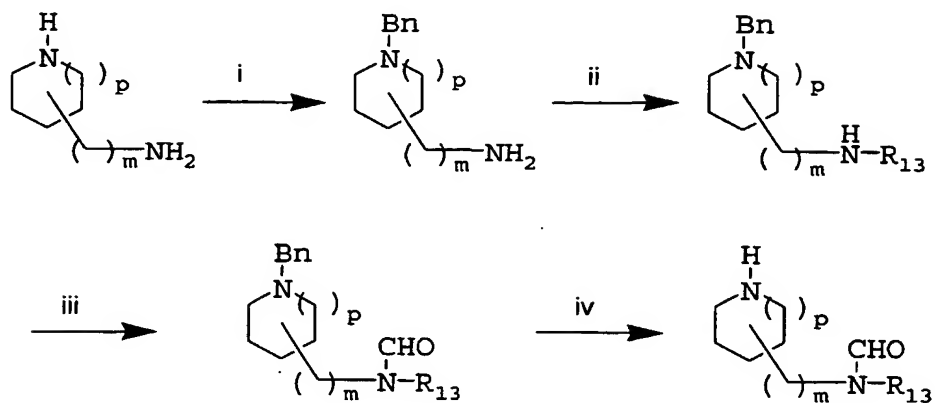
Scheme 1E. Synthesis of Side Chains

i) BOC_2O , CH_2Cl_2 , DIEA; ii) acid chloride followed by reduction with B_2H_6 ; DIEA; iii) A formylating agent such as 1H-benzotriazole-1-carboxaldehyde; iv) TFA, CH_2Cl_2

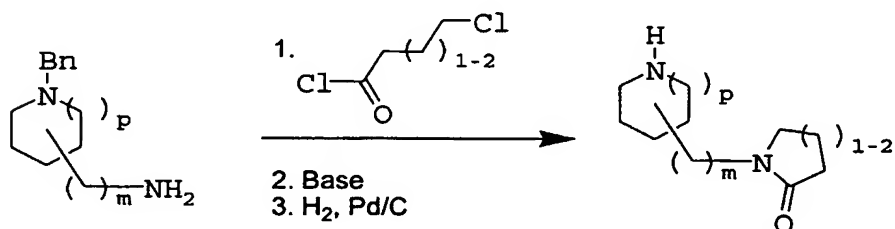


R_{13} , m , and p are substituents described herein

Scheme 1F. Synthesis of Side Chains

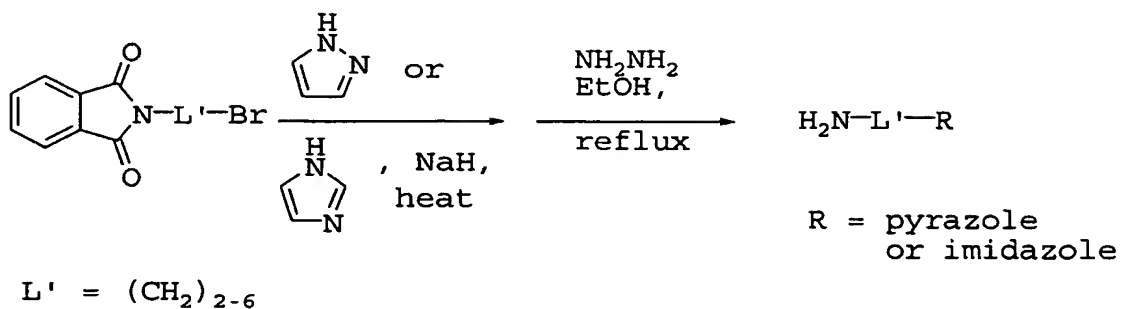


i) A protecting group such as BOC (using BOC_2O) or benzyl (Bn) using benzoyl chloride followed by reduction of the amide; ii) acid chloride followed by reduction with B_2H_6 ; iii) A formylating agent such as 1H-benzotriazole-1-carboxaldehyde; iv) H_2 , Pd/C

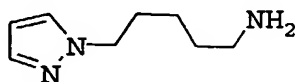


R_{13} , m , and p are substituents described herein

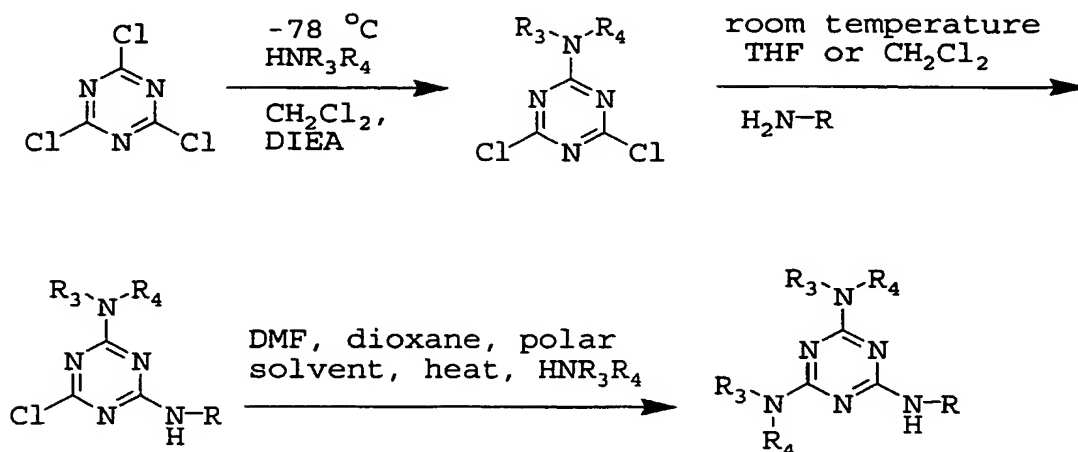
Scheme 1G. Synthesis of Side Chains



Example:



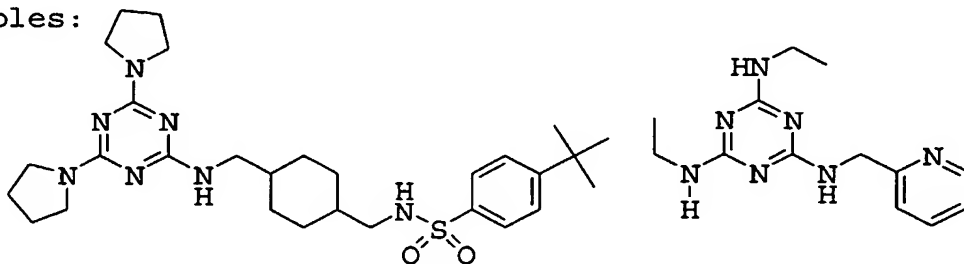
Scheme 2. Synthesis of Triaminotriazines



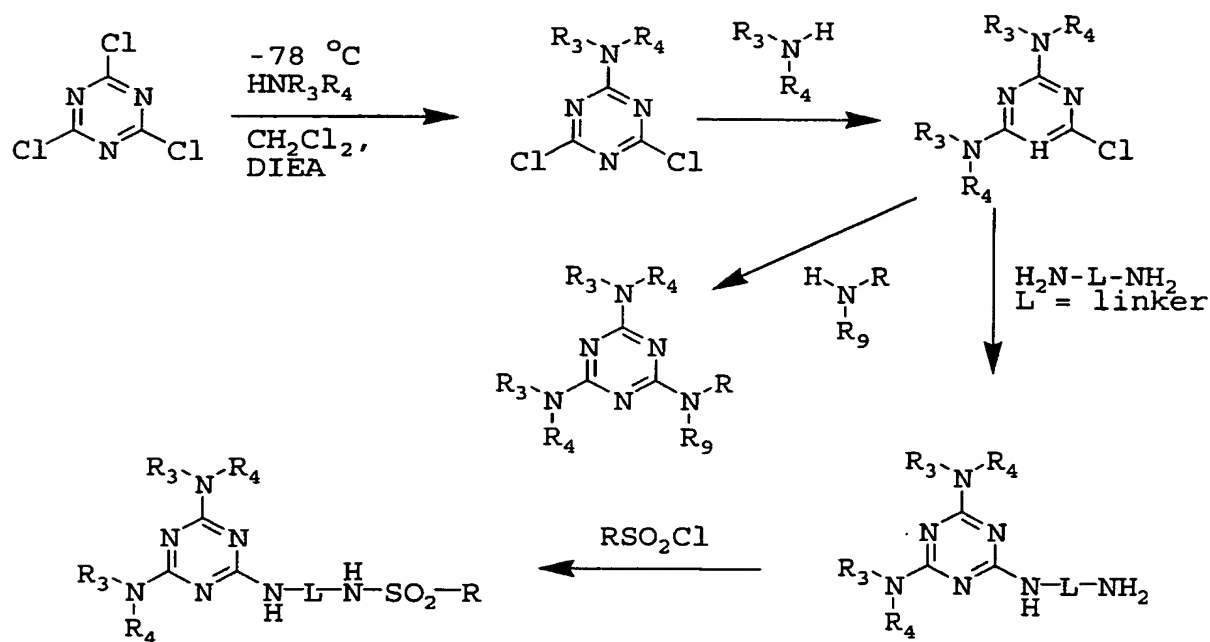
R_3 and R_4 are substituents described herein

$-\text{NHR}$ is a subset of the substituent R_8 described herein

Examples:



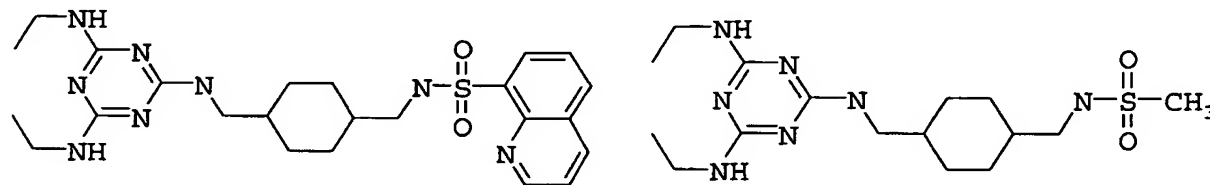
Scheme 3. Synthesis of Triaminotriazines

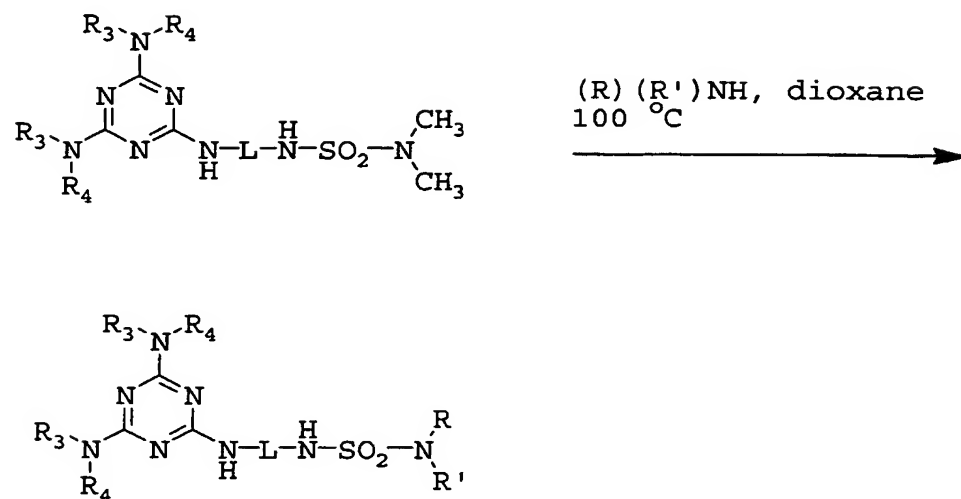


R_3 and R_4 are substituents described herein

$-\text{N(R}_9\text{)R}$ and $-\text{NH-L-NHSO}_2\text{-R}$ are independently subsets of the substituent R_8 described herein

Examples:

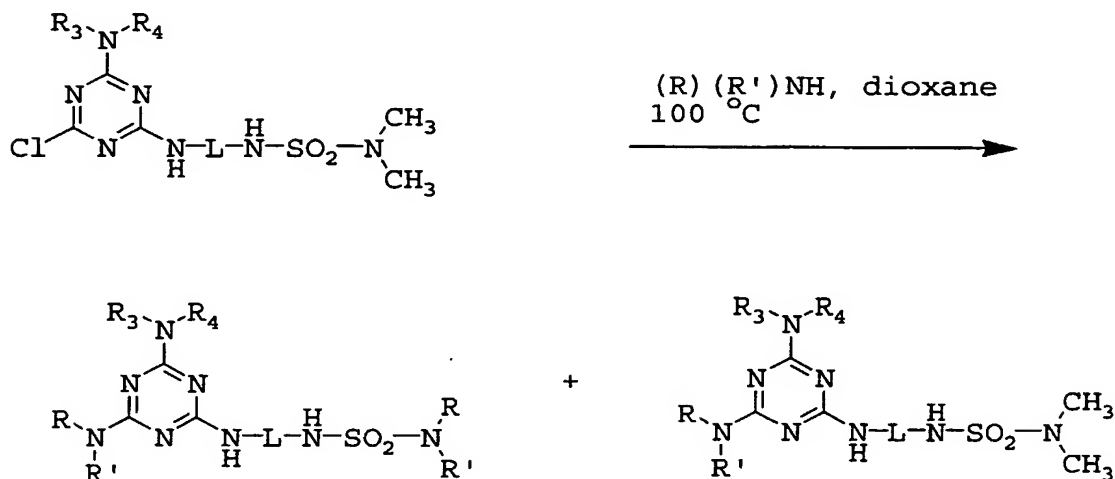


Scheme 4A. Synthesis of Triazine Derivatives

(R)(R')NH = morpholine, piperidine,
pyrrolidine, cyclopropylamine, etc.

-NH-L-NH-SO₂-N(R)(R') is a subset of
the R₈ substituent described herein

Scheme 4B. Synthesis of Triazine Derivatives

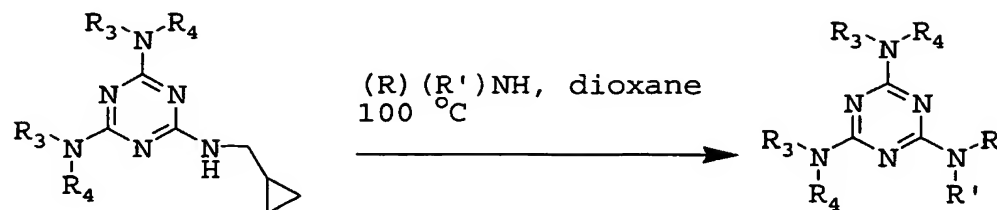
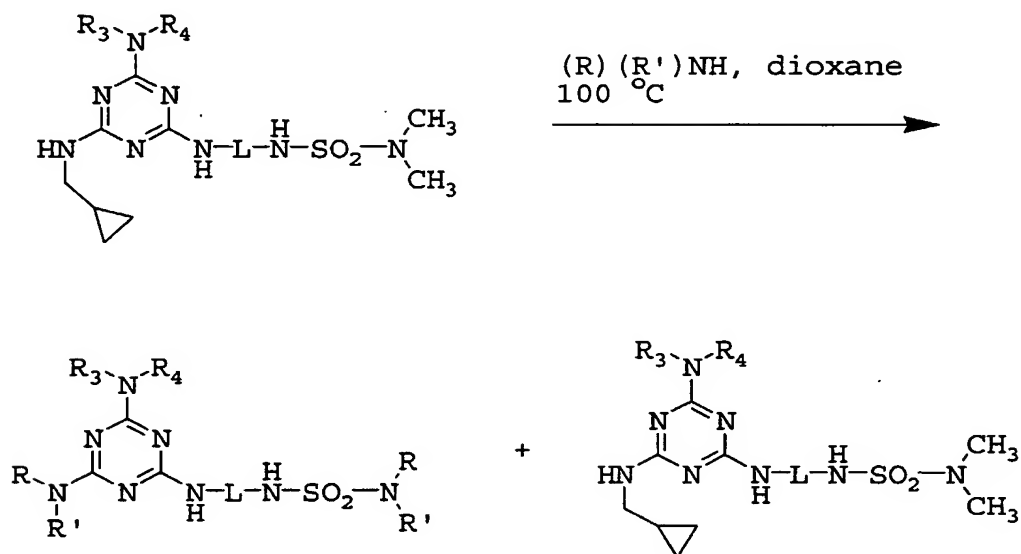


R_3 and R_4 are substituents described herein

$(\text{R})(\text{R}')\text{NH}$ = morpholine, piperidine, pyrrolidine, cyclopropylamine, etc.

$(\text{R})(\text{R}')\text{N-}$ = morpholinyl, piperidinyl, pyrrolidinyl, cyclopropylamine, etc.

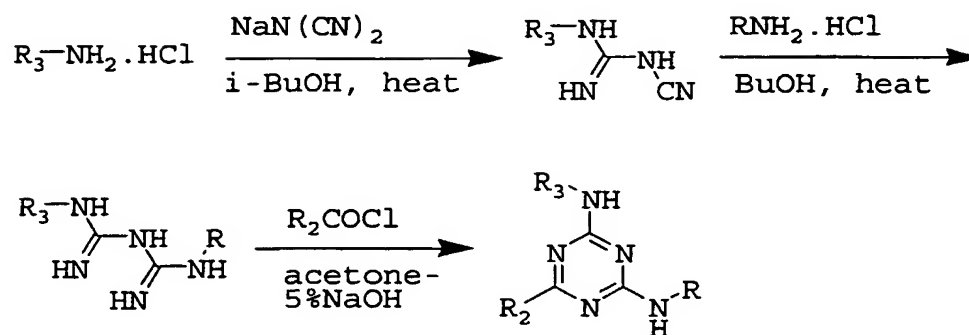
$-\text{NH-L-NH-SO}_2-\text{N(R)(R')}$ and $-\text{NH-L-NH-SO}_2-\text{N(CH}_3)_2$ are independently subsets of the R_8 substituent described herein

Scheme 4C. Synthesis of Triazine Derivatives**Scheme 4D. Synthesis of Triazine Derivatives**

R_3 and R_4 are substituents described herein

$(R)(R')NH$ = morpholine, piperidine, pyrrolidine, cyclopropylamine, etc.

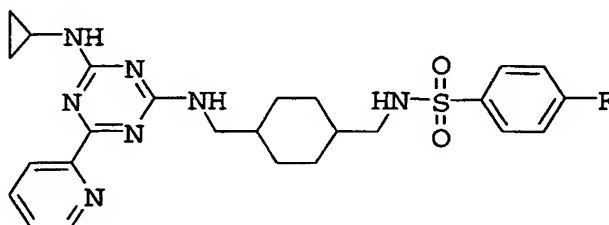
$-N(R)(R')$, $-NH-L-NHSO_2NR(R')$, and $-NH-L-NHSO_2N(CH_3)_2$ are subsets of the R_8 substituent described herein

Scheme 5. Synthesis of Diamino-1,3,5-triazines

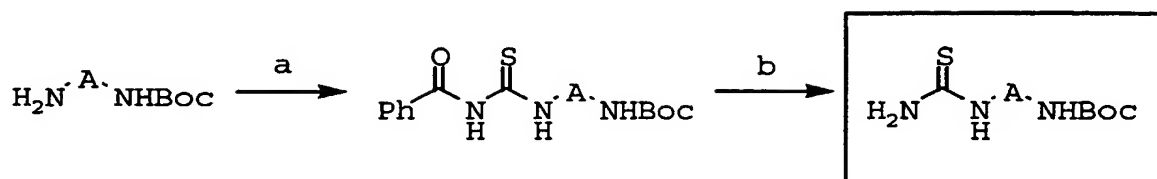
R_2 and R_3 are substituents described herein

-NH-R is a subset of the R_8 substituent described herein

Example:

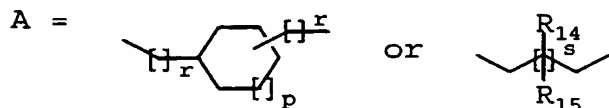


Scheme 6A. Synthesis of Thioureas 216

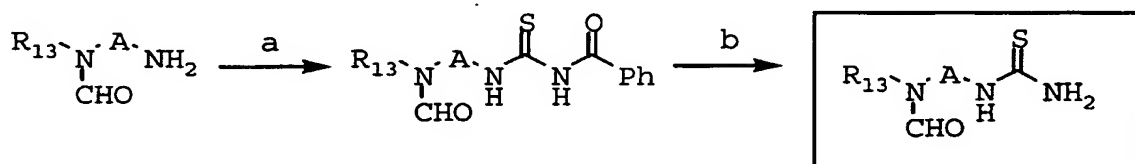


a. benzoylisothiocyanate

b. K_2CO_3 , MeOH



Scheme 6B. Synthesis of Thioureas



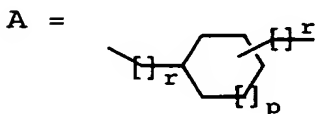
a. benzoylisothiocyanate

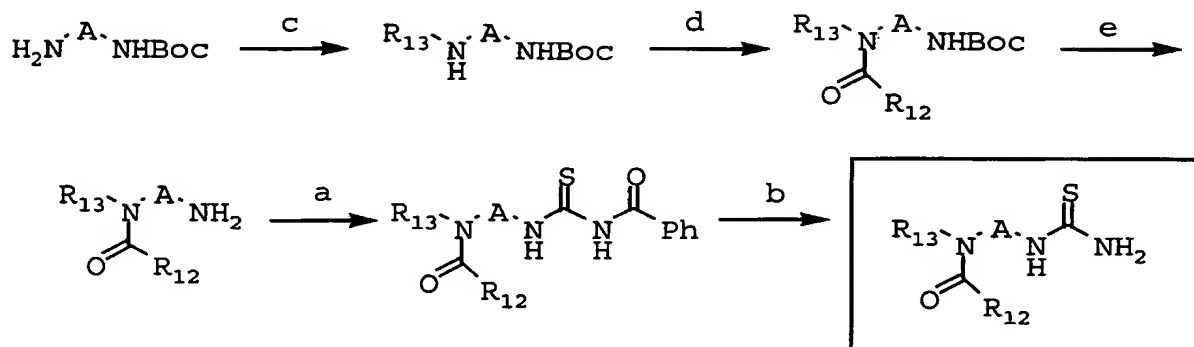
b. K_2CO_3 , MeOH

c. alkyl halide or acyl halide followed by borane reduction

d. formylating agent such as 1H-benzotriazole-1-carboxaldehyde

e. HCl or TFA



Scheme 6C. Synthesis of Thioureas

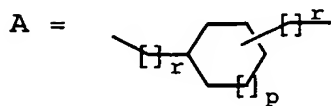
a. benzoylisothiocyanate

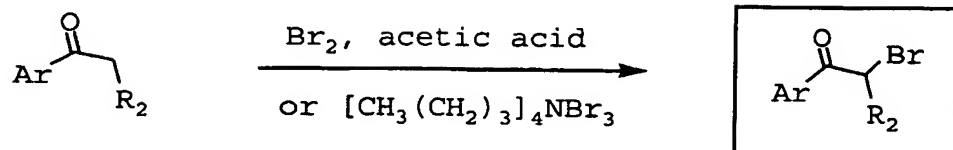
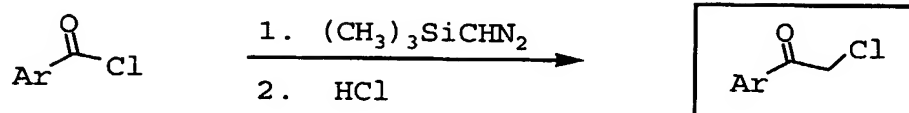
b. K_2CO_3 , MeOH

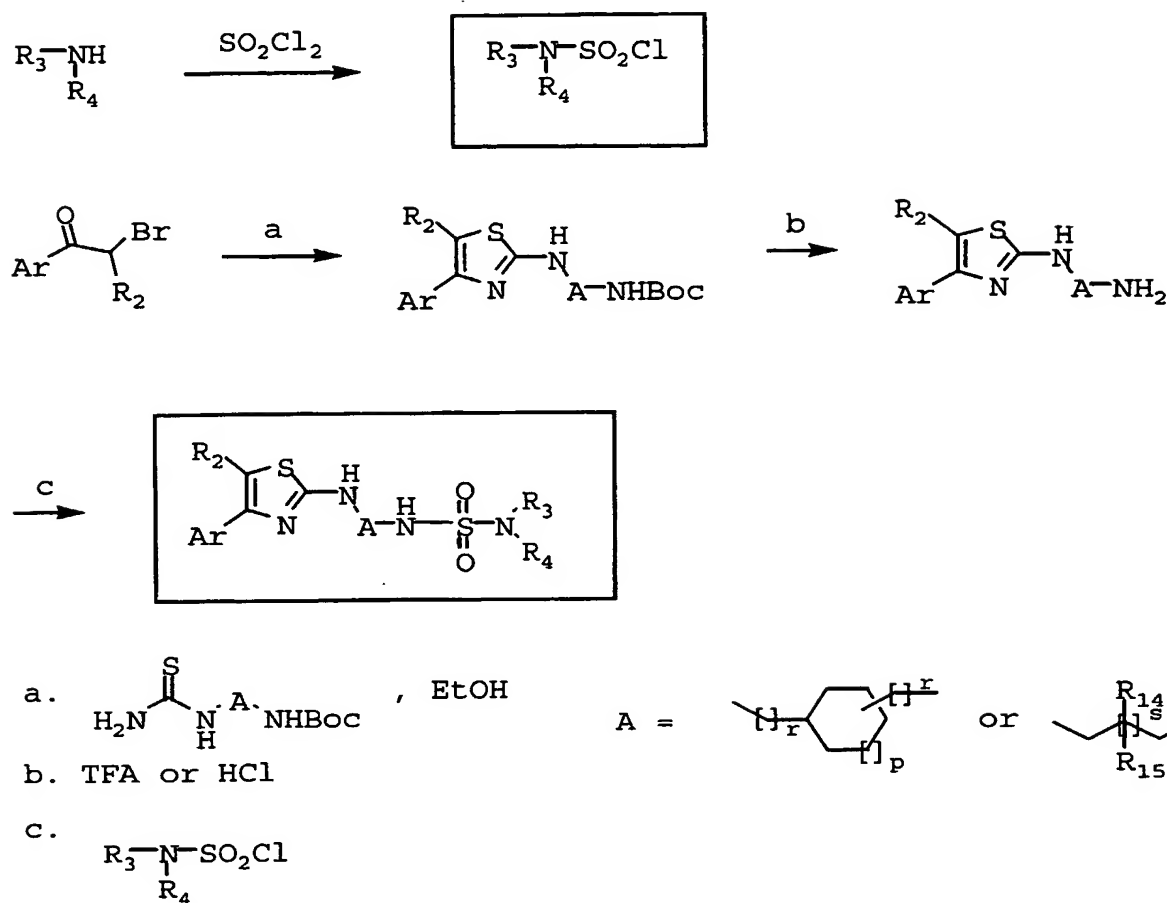
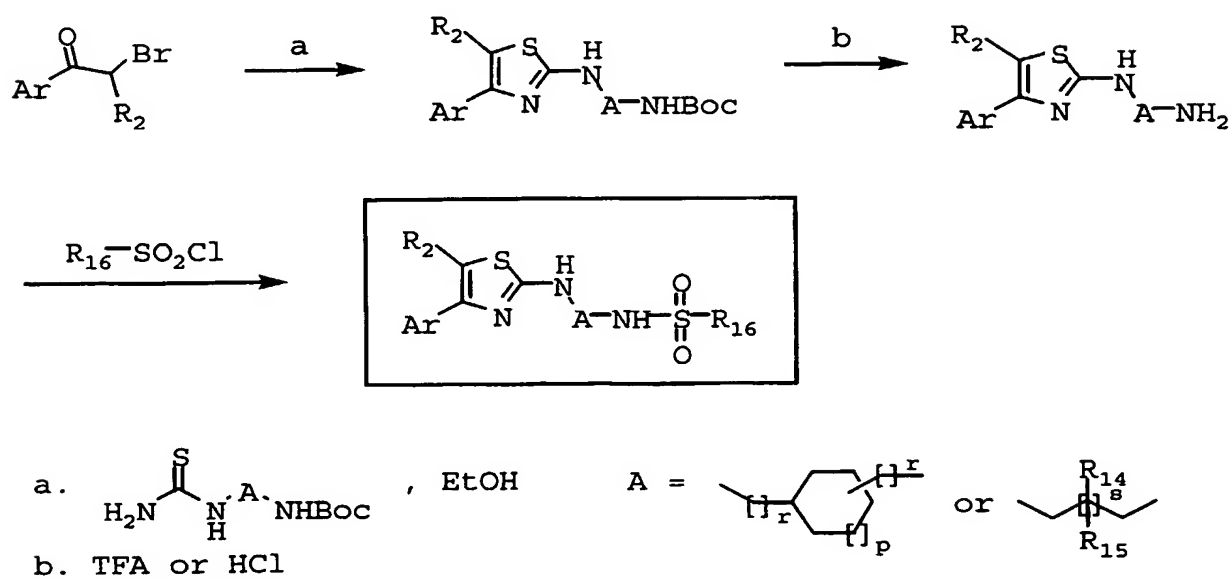
c. alkyl halide or acyl halide followed by borane reduction

d. R_{12}COCl

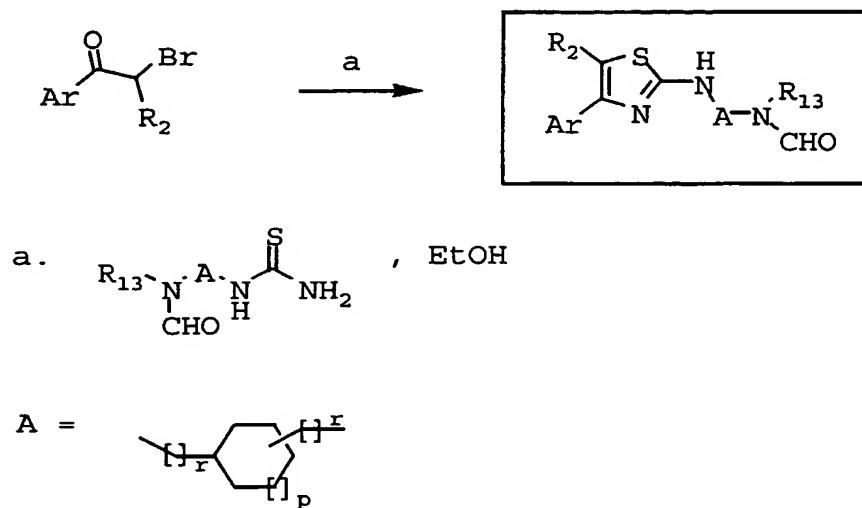
e. HCl or TFA



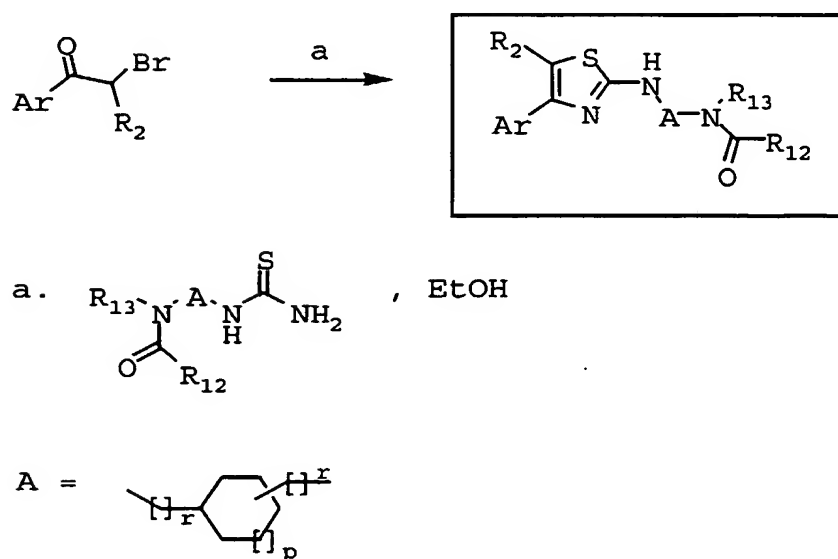
Scheme 7A. Synthesis of Bromoketones**Scheme 7B. Synthesis of Chloroketones**

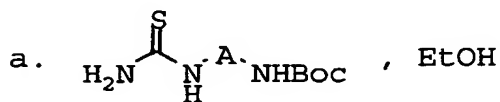
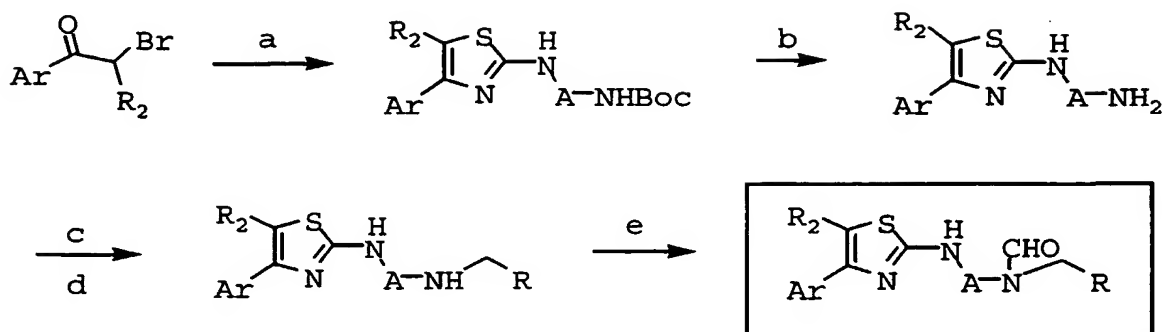
Scheme 8A. Synthesis of Bicycles**Scheme 8B. Synthesis of Bicycles**

Scheme 8C. Synthesis of Bicycles



Scheme 8D. Synthesis of Bicycles



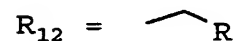
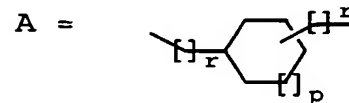
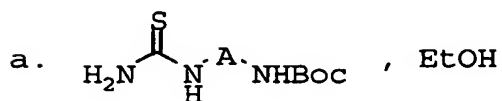
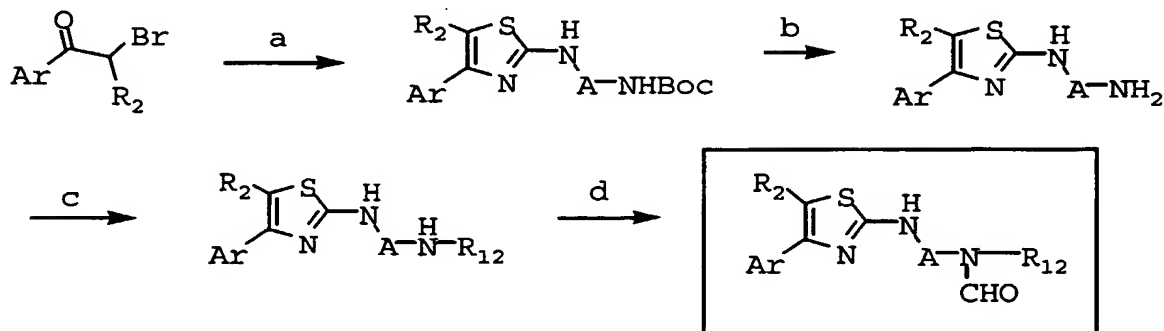
Scheme 8E. Synthesis of Bicycles

b. TFA or HCl

c. RCOCl

d. reduction

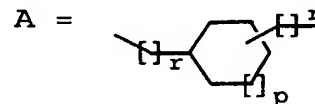
e. formylating agent such as 1H-benzotriazole-1-carboxaldehyde

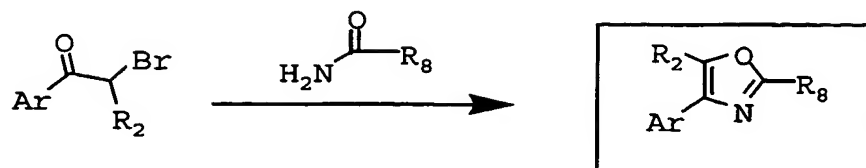
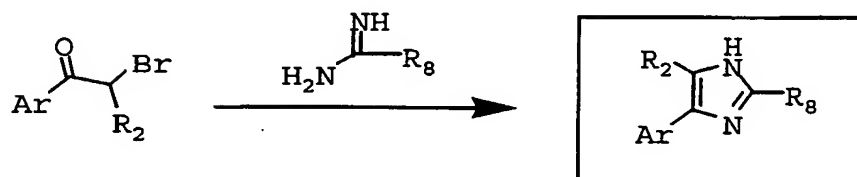
**Scheme 8F. Synthesis of Bicycles**

b. TFA or HCl

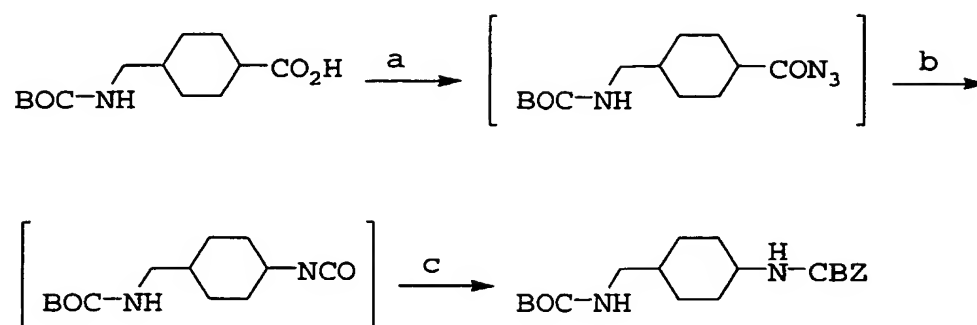
c. R₁₂I

d. formylating agent such as 1H-benzotriazole-1-carboxaldehyde



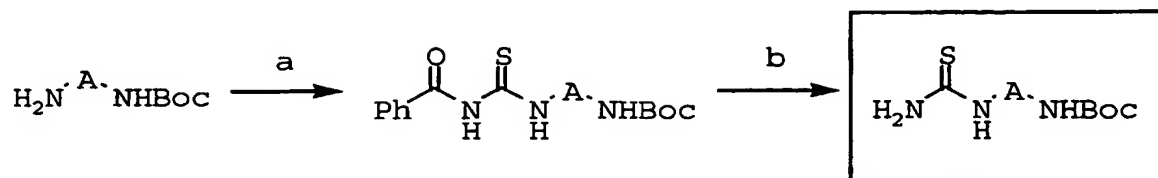
Scheme 9A. Synthesis of Bicycles**Scheme 9B. Synthesis of Bicycles**

Scheme 10: Synthesis of Side Chains



a. Diphenylphosphoryl azide, triethylamine, toluene;
b. heat; c. HOCH_2Ph

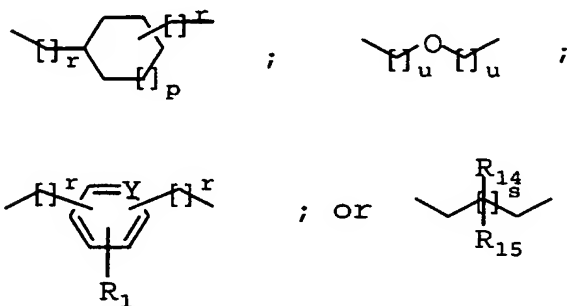
Scheme 11A. Synthesis of Thioureas



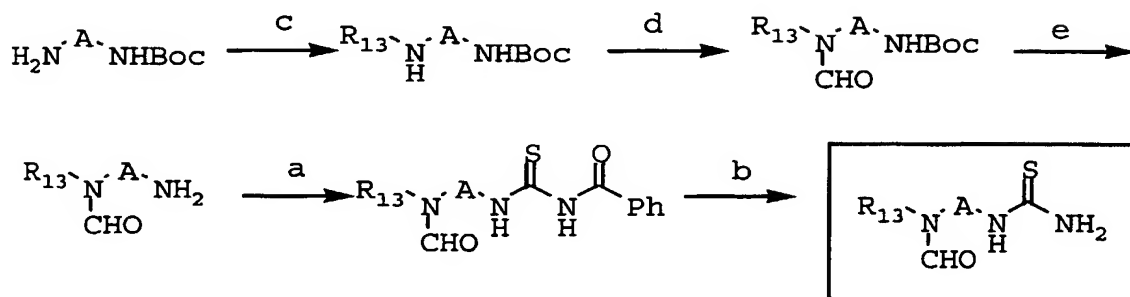
a. benzoylisothiocyanate

b. K_2CO_3 , MeOH

A =



Scheme 11B. Synthesis of Thioureas



a. Benzoylisothiocyanate

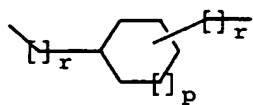
b. K_2CO_3 , MeOH

c. alkyl halide or acyl halide followed by borane reduction

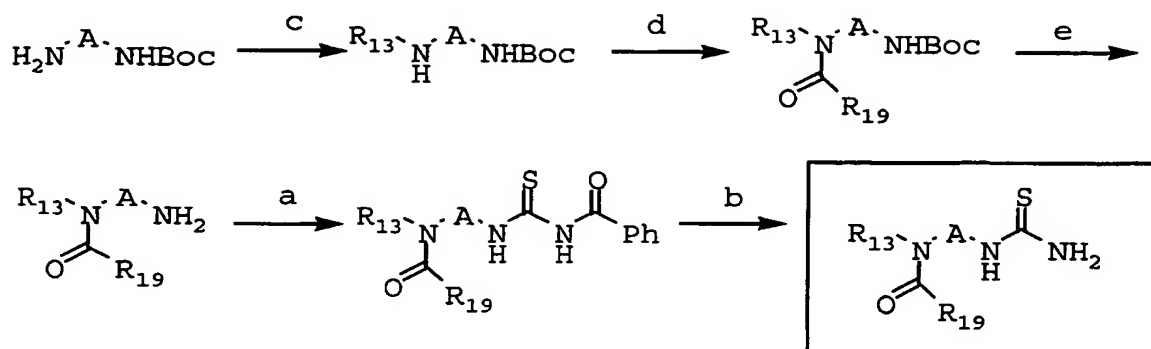
d. formylating agent such as 1H-benzotriazole-1-carboxaldehyde

e. HCl or TFA

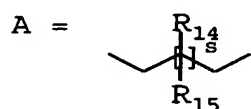
A =



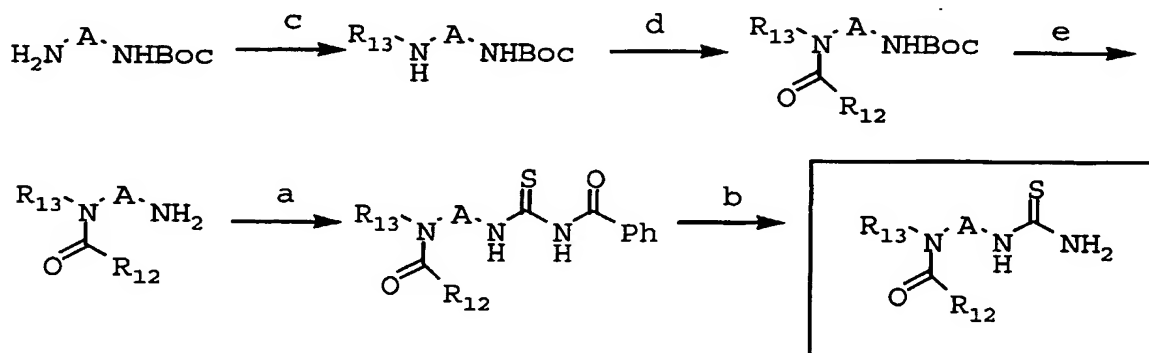
Scheme 11C. Synthesis of Thioureas



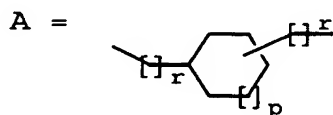
- Benzoylisothiocyanate
- K_2CO_3 , MeOH
- alkyl halide or acyl halide followed by borane reduction
- $R_{19}COCl$
- HCl or TFA



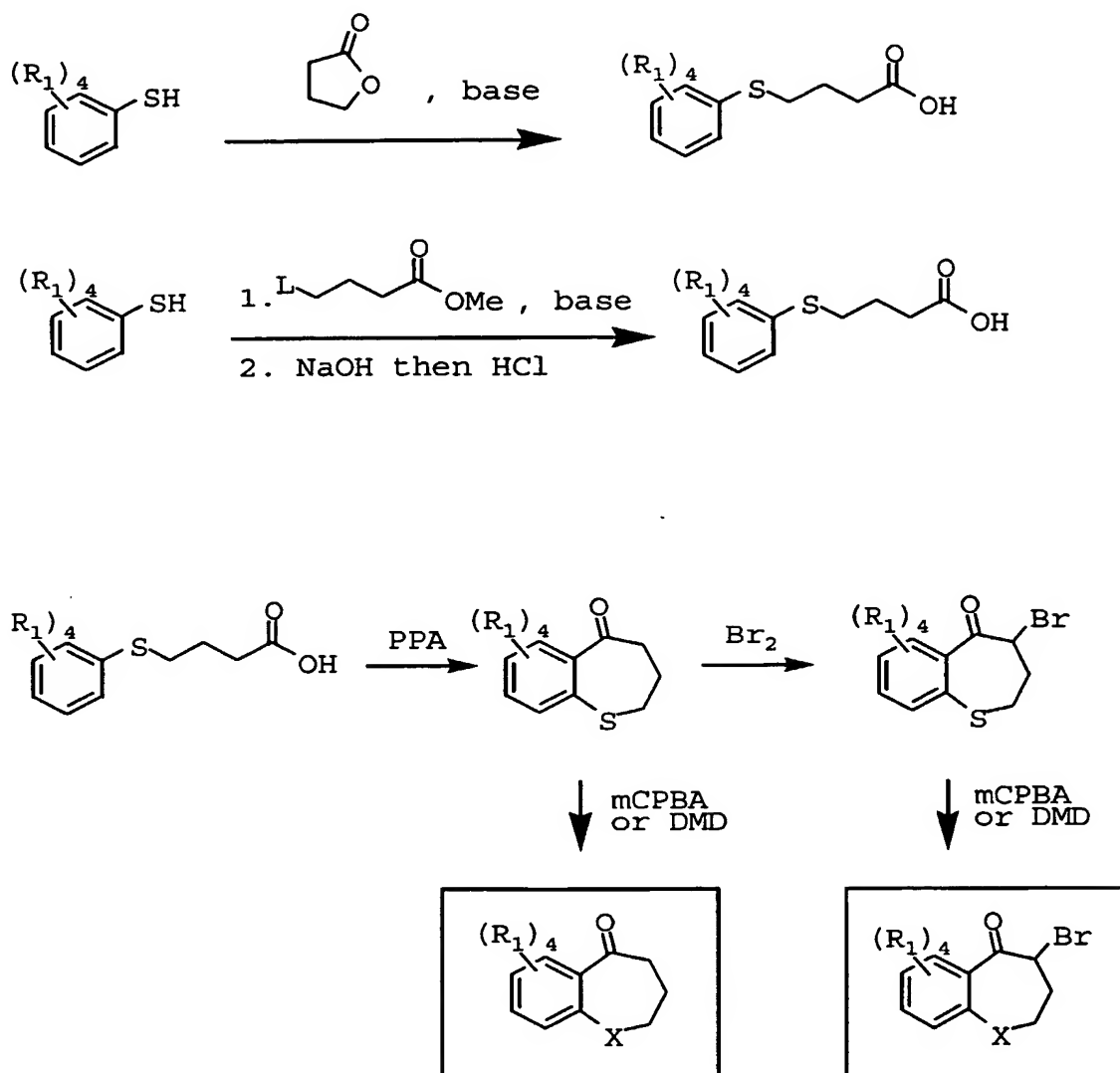
Scheme 11D. Synthesis of Thioureas



- Benzoylisothiocyanate
- K_2CO_3 , MeOH
- alkyl halide or acyl halide followed by borane reduction
- $R_{12}COCl$
- HCl or TFA



Scheme 12. Synthesis of Bromoketones

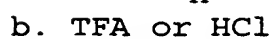
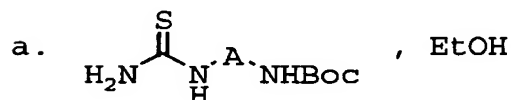
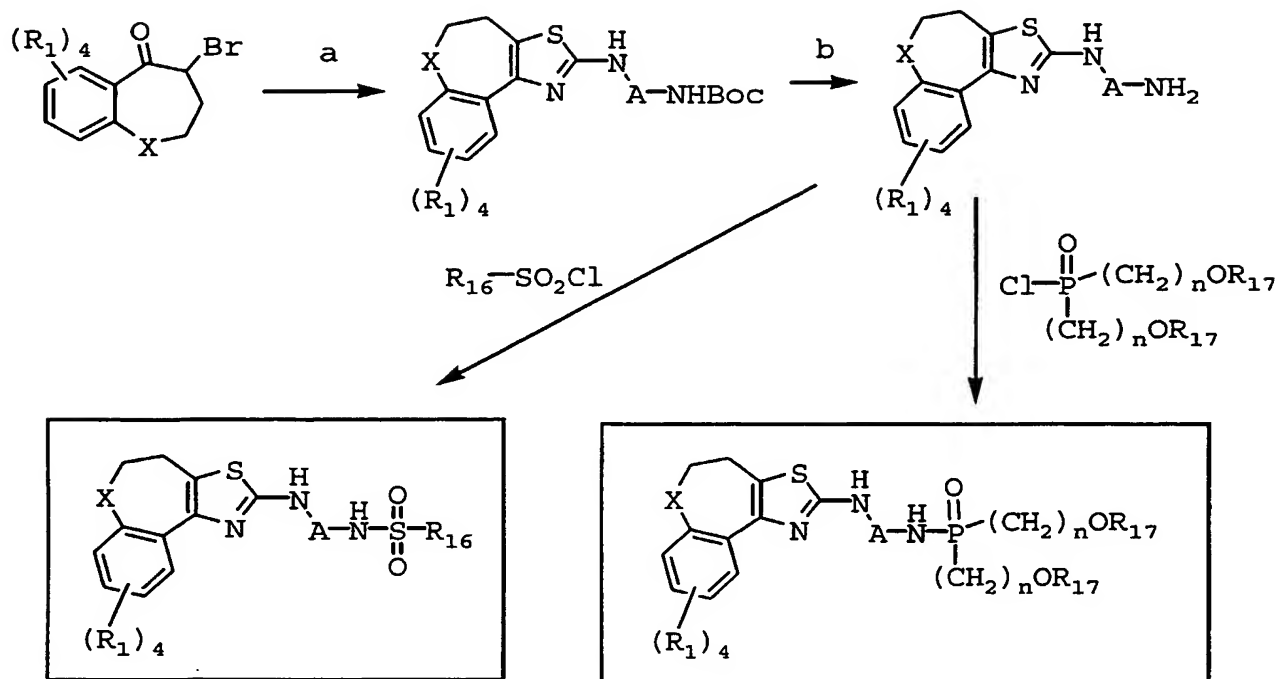


L = leaving group such as Br

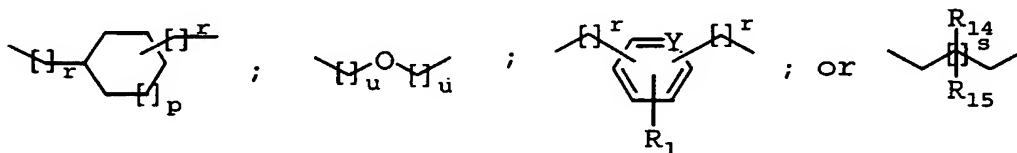
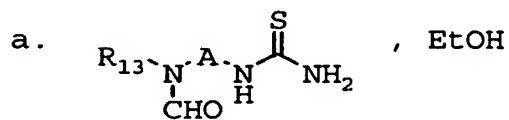
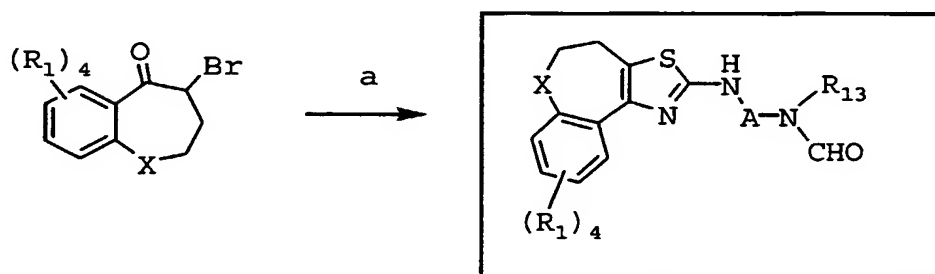
X = S, SO, SO₂

DMD = dimethyldioxirane

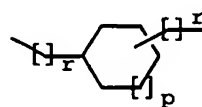
mCPBA = m-chloroperbenzoic acid

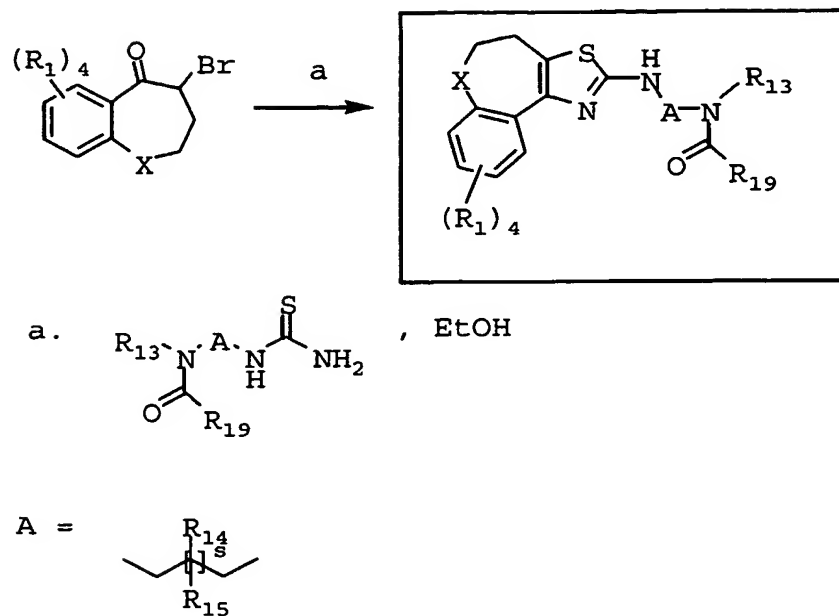
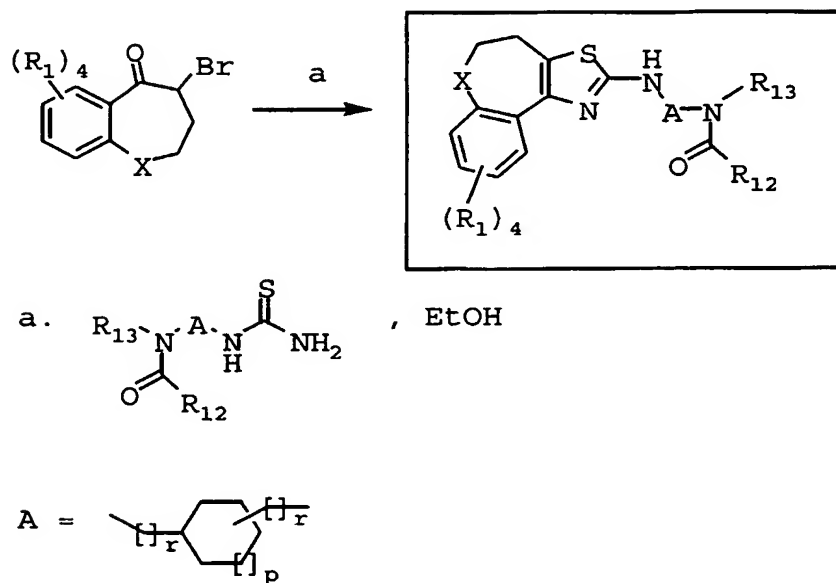
Scheme 13A. Synthesis of the Tricycles

A =

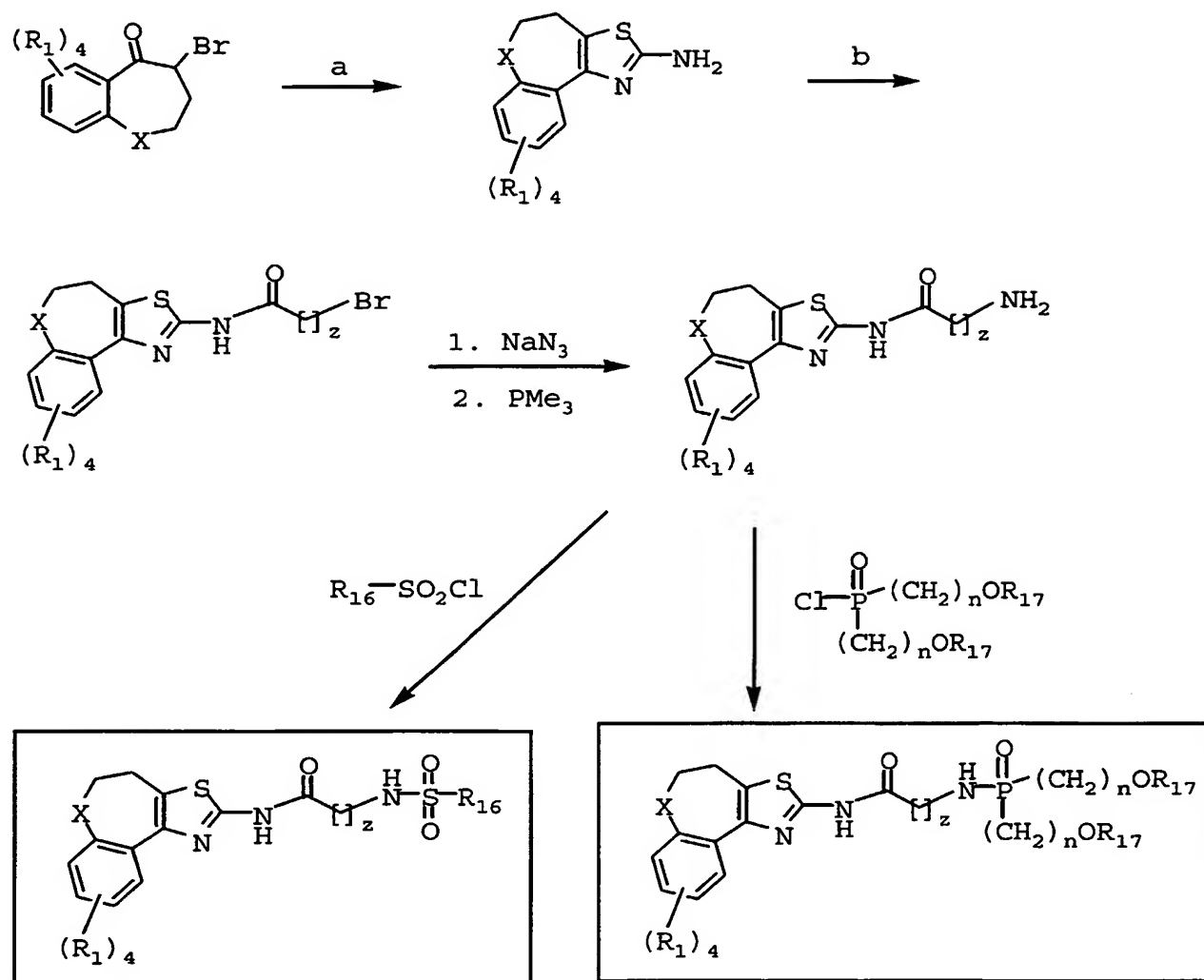
**Scheme 13B. Synthesis of the Tricycles**

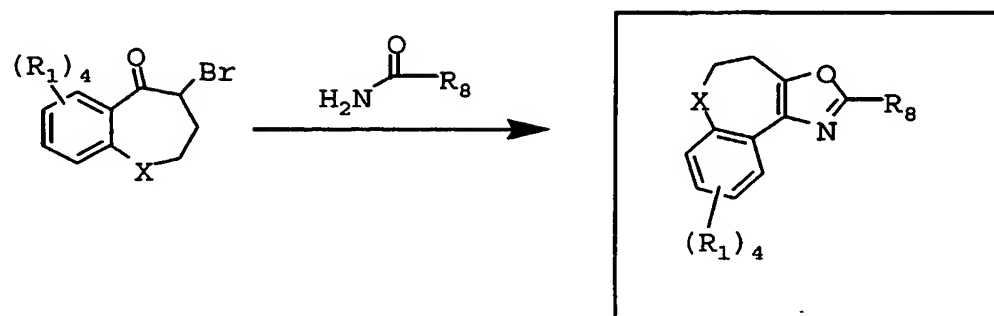
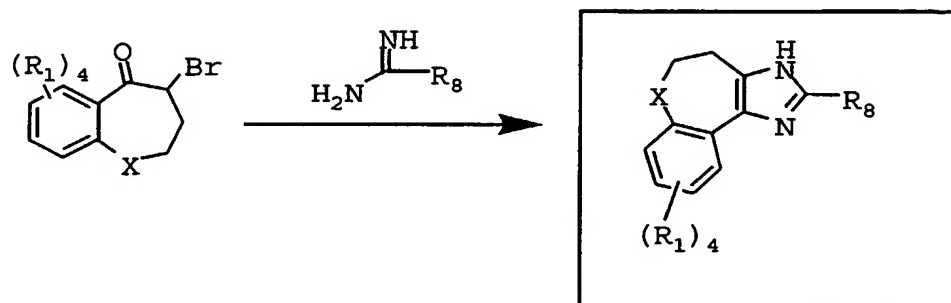
A =

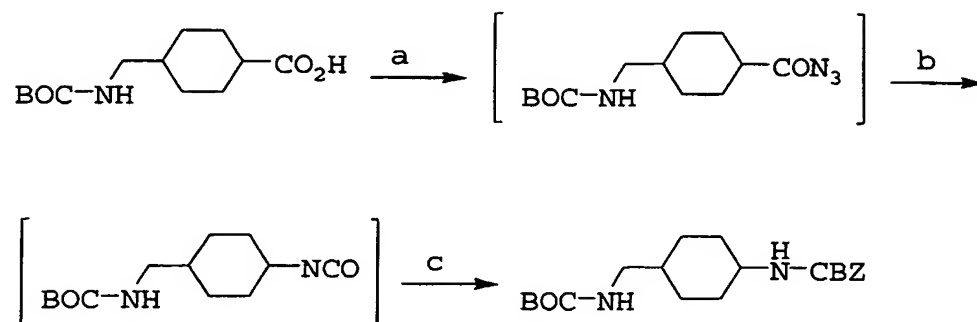


Scheme 13C. Synthesis of the Tricycles**Scheme 13D. Synthesis of the Tricycles**

Scheme 13E. Synthesis of the Tricycles



Scheme 14A. Synthesis of Tricycles**Scheme 14B. Synthesis of Tricycles**

Scheme 15: Synthesis of Side Chains

a. Diphenylphosphoryl azide, triethylamine, toluene;
b. heat; c. HOCH_2Ph

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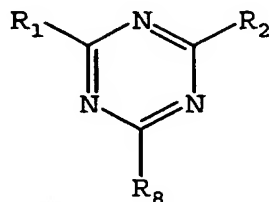
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15 Wahlestedt, C., and Reis, D. J. (1993). Neuropeptide
Y-Related Peptides and Their Receptors--Are the Receptors
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20 Zhao, Z., et al., "Synthesis of trans-4-Alkenyloxazoles"
Tetrahedron. Lett. (1991) 32(13): 1609-1612.

What is claimed is:

1. A compound having the structure



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wherein R_1 is F; Cl; Br; I; NR_3R_4 ; or phenyl or heteroaryl; wherein the phenyl or heteroaryl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nC(Y)R₇, -(CH₂)_nYR₅, -(CH₂)_nC(Y)NR₅R₆, -(CH₂)_nNR₅C(Y)R₅, -(CH₂)_nCO₂R₅, -(CH₂)_nSO₂NR₅R₆, a straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, C₂-C₇ alkenyl or C₂-C₇ alkynyl, or a C₃-C₇ cycloalkyl or cycloalkenyl;

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wherein R_2 is NR_3R_4 ;

wherein R_3 is independently H; -(CH₂)_uYR₅; -(CH₂)_tC(Y)NR₅R₆; -(CH₂)_uNR₅C(Y)R₅; -(CH₂)_tC(Y)R₇; -(CH₂)_tCO₂R₅; -(CH₂)_uNR₅R₆; -(CH₂)_uCN; -C(Y)R₅; -C(Y)NR₅R₆; -CO₂R₅; straight chained or branched C₁-C₇ alkyl, C₂-C₇ alkenyl, or C₂-C₇ alkynyl; C₃-C₇ cycloalkyl or cycloalkenyl; phenyl; C₁-C₆ phenylalkyl; or C₁-C₆ heteroarylalkyl; wherein the phenyl, C₁-C₆ phenylalkyl, or C₁-C₆ heteroarylalkyl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nC(Y)R₇, -(CH₂)_nYR₅, -(CH₂)_nC(Y)NR₅R₆, -(CH₂)_nNR₅C(Y)R₅, -(CH₂)_nCO₂R₅, -(CH₂)_nSO₂NR₅R₆, a straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl,

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C₂-C₇ alkenyl or C₂-C₇ alkynyl, or a C₃-C₇ cycloalkyl or cycloalkenyl;

wherein R₄ is independently H; -(CH₂)_uYR₅; -
 5 (CH₂)_tC(Y)NR₅R₆; -(CH₂)_uNR₅C(Y)R₅; -(CH₂)_tC(Y)R₇; -
 (CH₂)_tCO₂R₅; -(CH₂)_uNR₅R₆; -(CH₂)_uCN; straight chained or
 branched C₁-C₇ alkyl; straight chained or branched C₂-
 C₇ alkenyl or C₂-C₇ alkynyl; C₃-C₇ cycloalkyl or
 cycloalkenyl; phenyl; or C₁-C₆ phenylalkyl; wherein
 10 the phenyl or C₁-C₆ phenylalkyl may be substituted
 with one or more of F, Cl, Br, I, -CN, -NO₂, -
 NR₅R₆, -SO₂R₅, -(CH₂)_nC(Y)R₇, -(CH₂)_nYR₅, -
 (CH₂)_nC(Y)NR₅R₆, -(CH₂)_nNR₅C(Y)R₅, -(CH₂)_nCO₂R₅, -
 (CH₂)_nSO₂NR₅R₆, a straight chained or branched C₁-C₇
 15 alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl,
 C₂-C₇ alkenyl or C₂-C₇ alkynyl, or a C₃-C₇ cycloalkyl
 or cycloalkenyl;

or R₃ and R₄ taken together with the nitrogen atom to
 20 which they are attached are 1-azetidiny, 1-
 pyrrolidiny, 1-piperidiny, or 1H-azepany, wherein
 the 1-azetidiny, 1-pyrrolidiny, 1-
 piperidiny, or 1H-azepany is substituted with one
 or more of F, -CN, -(CH₂)_nNR₅R₆, -SO₂R₅, -
 25 (CH₂)_nC(Y)R₇, -(CH₂)_nYR₅, -(CH₂)_nC(Y)NR₅R₆, -
 (CH₂)_nNR₅C(Y)R₅, -(CH₂)_nCO₂R₅, a straight chained or
 branched C₁-C₇ alkyl, monofluoroalkyl,
 polyfluoroalkyl, aminoalkyl, a C₂-C₇ alkenyl or C₂-C₇
 alkynyl, a C₃-C₇ cycloalkyl or cycloalkenyl, or phenyl
 30 or heteroaryl; wherein if -(CH₂)_nNR₅R₆, -
 (CH₂)_nYR₅, or -(CH₂)_nNR₅C(Y)R₅ are in the 2-position,
 then n is not 0; wherein the phenyl or heteroaryl may
 be substituted with one or more of F, Cl, Br, I, -
 CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nC(Y)R₇, -
 35 (CH₂)_nYR₅, -(CH₂)_nC(Y)NR₅R₆, -(CH₂)_nNR₅C(Y)R₅, -

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$(\text{CH}_2)_n\text{CO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{SO}_2\text{NR}_5\text{R}_6$, a straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, a C_2 - C_7 alkenyl or C_2 - C_7 alkynyl, or a C_3 - C_7 cycloalkyl or cycloalkenyl;

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or R_3 and R_4 taken together with the nitrogen atom to which they are attached are morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl, wherein the morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl is substituted with one or more straight chained or branched C_1 - C_7 alkyl or C_1 - C_7 phenylalkyl; and wherein the nitrogen atom of the piperazinyl or [1,4]diazepanyl ring is substituted with -
 $(\text{CH}_2)_u\text{YR}_5$; $-(\text{CH}_2)_t\text{C}(\text{Y})\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{NR}_5\text{C}(\text{Y})\text{R}_5$; $-(\text{CH}_2)_t\text{C}(\text{Y})\text{R}_7$; $-(\text{CH}_2)_t\text{CO}_2\text{R}_5$; $-(\text{CH}_2)_u\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{CN}$; $-\text{C}(\text{Y})\text{R}_5$; $-\text{C}(\text{Y})\text{NR}_5\text{R}_6$; $-\text{CO}_2\text{R}_5$; straight chained or branched C_1 - C_7 alkyl, C_2 - C_7 alkenyl, or C_2 - C_7 alkynyl; or C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl; C_1 - C_6 phenylalkyl; or C_1 - C_6 heteroarylalkyl; wherein the phenyl, C_1 - C_6 phenylalkyl, or C_1 - C_6 heteroarylalkyl may be substituted with one or more of F, Cl, Br, I, -CN, - NO_2 , - NR_5R_6 , - SO_2R_5 , $-(\text{CH}_2)_n\text{C}(\text{Y})\text{R}_7$, $-(\text{CH}_2)_n\text{YR}_5$, $-(\text{CH}_2)_n\text{C}(\text{Y})\text{NR}_5\text{R}_6$, $-(\text{CH}_2)_n\text{NR}_5\text{C}(\text{Y})\text{R}_5$, $-(\text{CH}_2)_n\text{CO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{SO}_2\text{NR}_5\text{R}_6$, a straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, a C_2 - C_7 alkenyl or C_2 - C_7 alkynyl, or a C_3 - C_7 cycloalkyl or cycloalkenyl;

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wherein each of R_5 , R_6 and R_7 is independently H; or straight chained or branched C_1 - C_7 alkyl;

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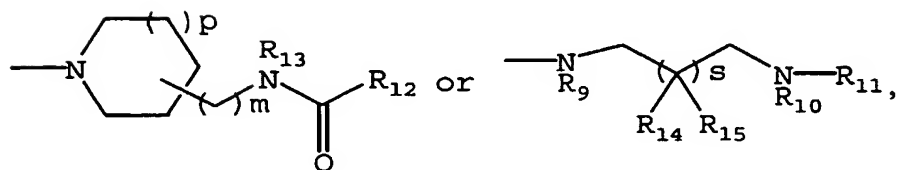
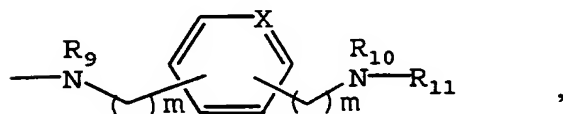
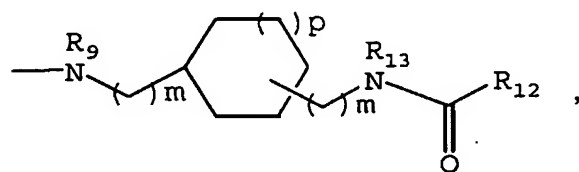
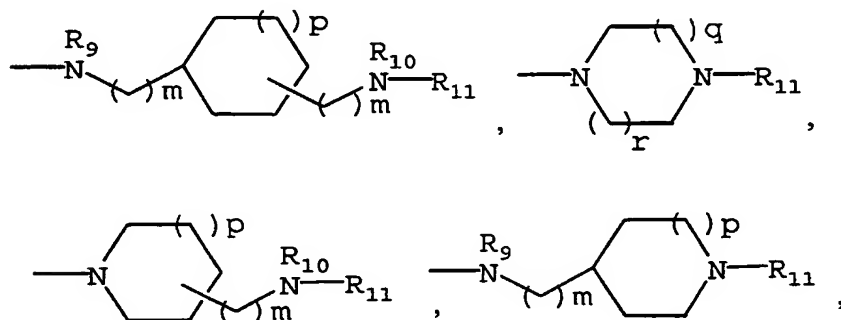
wherein each n is independently an integer from 0 to 6 inclusive;

wherein each t is independently an integer from 1 to 4 inclusive;

wherein each u is independently an integer from 2 to 4 inclusive;

wherein Y is O or S;

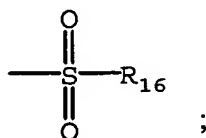
wherein R₈ is



provided that if R_8 ²⁴³ contains a piperidinyl group and m is 0, then the compound is not an -aminal-containing compound;

wherein each of R_9 and R_{10} is independently H; straight chained or branched C_1 - C_4 alkyl;

wherein R_{11} is H or



wherein R_{12} is H;

wherein R_{13} is independently H; $-(\text{CH}_2)_u\text{YR}_5$; $-(\text{CH}_2)_t\text{C}(\text{Y})\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{NR}_5\text{C}(\text{Y})\text{R}_5$; $-(\text{CH}_2)_t\text{C}(\text{Y})\text{R}_7$; $-(\text{CH}_2)_t\text{CO}_2\text{R}_5$; $-(\text{CH}_2)_u\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{CN}$; $-\text{C}(\text{Y})\text{R}_5$; $-\text{C}(\text{Y})\text{NR}_5\text{R}_6$; $-\text{CO}_2\text{R}_5$; straight chained or branched C_1 - C_7 alkyl; C_1 - C_7 alkyl substituted with one or more F or Cl; C_3 - C_7 cycloalkyl- C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl, or alkynyl; or C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl or C_1 - C_6 phenylalkyl; wherein the phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F, Cl, $-\text{CN}$, $-\text{NO}_2$, $-\text{NR}_5\text{R}_6$, $-\text{SO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{C}(\text{Y})\text{R}_7$, $-(\text{CH}_2)_n\text{YR}_5$, $-(\text{CH}_2)_n\text{C}(\text{Y})\text{NR}_5\text{R}_6$, $-(\text{CH}_2)_n\text{NR}_5\text{C}(\text{Y})\text{R}_5$, $-(\text{CH}_2)_n\text{CO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{SO}_2\text{NR}_5\text{R}_6$, a straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, a C_2 - C_7 alkenyl or C_2 - C_7 alkynyl, or a C_3 - C_7 cycloalkyl or cycloalkenyl;

or R_{12} and R_{13} together with the amide linkage to which they are attached are pyrrolidinonyl or piperidonyl;

5 wherein R_{14} is H; straight chained or branched C_1 - C_7 alkyl; F; or $-(CH_2)_nOR_5$;

wherein R_{15} is H, straight chained or branched C_1 - C_7 alkyl, or F;

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wherein R_{16} is NR_3R_4 , unsubstituted straight chained or branched C_2 - C_7 alkyl, substituted straight chained or branched C_1 - C_7 alkyl, wherein the C_1 - C_7 alkyl may be substituted with one or more of F, Cl, -CN, $-NR_5R_6$, $-SO_2R_5$, $-(CH_2)_nC(Y)R_7$, $-(CH_2)_nYR_5$, $-(CH_2)_nC(Y)NR_5R_6$, $-(CH_2)_nNR_5C(Y)R_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nOCF_3$,

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monofluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or C_2 - C_7 alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl, phenyl, heteroaryl, or C_1 - C_7 phenylalkyl, wherein the phenyl, heteroaryl, or C_1 - C_7 phenylalkyl may be substituted with one or more of F, Cl, Br, I, -CN, $-NO_2$, $-NR_5R_6$, $-(CH_2)_nNR_5C(Y)R_5$, $-SO_2R_5$, $-(CH_2)_nC(Y)R_7$, $-(CH_2)_nYR_5$, $-(CH_2)_nC(Y)NR_5R_6$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy,

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straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl; quinolinyl, 1-naphthyl, 2-naphthyl, or 2,1,3-benzothiadiazolyl; with the provisos that when R_1 is F, Cl, Br, or I, then R_{16} is 1-naphthyl; and when R_1 and R_2 are morpholinyl, then R_{16} is not NR_3R_4 ;

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wherein each m is independently an integer from 0 to 3 inclusive;

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wherein each s is independently an integer from 1 to 6 inclusive;

wherein each p is independently an integer from 0 to 2 inclusive;

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wherein each q is independently an integer from 1 to 2 inclusive;

wherein each r is independently an integer from 1 to 2 inclusive;

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wherein X is N or C;

or a pharmaceutically acceptable salt thereof.

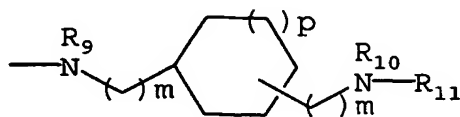
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2. The compound of claim 1, wherein the compound comprises the (+) enantiomer.

3. The compound of claim 1, wherein the compound comprises the (-) enantiomer.

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4. The compound of claim 1, wherein R_8 is



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5. The compound of claim 1, wherein R_1 is F, Cl, Br, I, or NR_3R_4 .

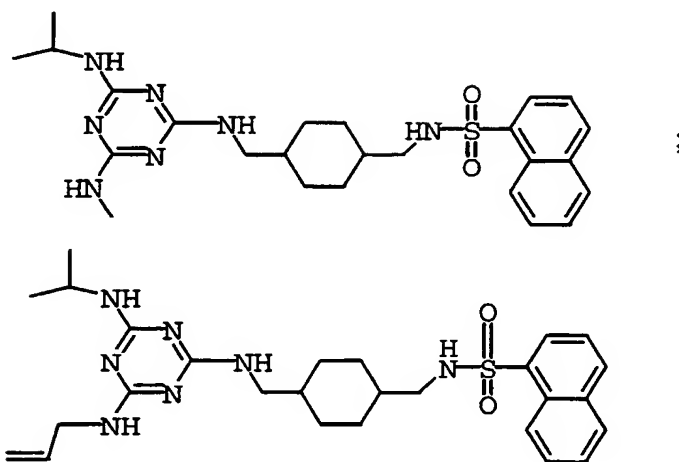
6. The compound of claim 1, wherein R_1 and R_2 are both NR_3R_4 where R_3 and R_4 are independently H; straight chained or branched C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or R_3 and R_4 taken together with the nitrogen atom to which they are attached are morpholinyl, piperazinyl, or 1-pyrrolidinyl, wherein the morpholinyl, piperazinyl, or 1-pyrrolidinyl is substituted with one or more straight chained or branched C_1 - C_7 alkyl or C_1 - C_7 phenylalkyl; and wherein the nitrogen atom of the piperazinyl ring is substituted with H; -
 (CH₂)_uYR₅; - (CH₂)_tC(Y)NR₅R₆; - (CH₂)_uNR₅C(Y)R₅; -
 (CH₂)_tC(Y)R₇; - (CH₂)_tCO₂R₅; - (CH₂)_uNR₅R₆; - (CH₂)_uCN; -
 C(Y)R₅; - C(Y)NR₅R₆; - CO₂R₅; straight chained or
 branched C_1 - C_7 alkyl; straight chained or branched C_2 -
 C_7 alkenyl or alkynyl; C_3 - C_7 cycloalkyl or
 cycloalkenyl; phenyl; C_1 - C_6 phenylalkyl; or C_1 - C_6
 heteroarylalkyl.
7. The compound of claim 1, wherein R_{16} is phenyl, 1-naphthyl, quinolinyl, or 2,1,3-benzothiadiazolyl; wherein the phenyl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -NR₅R₆, -
 (CH₂)_nNR₅C(Y)R₅, -SO₂R₅, - (CH₂)_nC(Y)R₇, - (CH₂)_nYR₅,
 - (CH₂)_nC(Y)NR₅R₆, - (CH₂)_nCO₂R₅, - (CH₂)_nSO₂NR₅R₆,
 ethylenedioxy, methylenedioxy, straight chained or
 branched C_1 - C_7 alkyl, monofluoroalkyl,
 polyfluoroalkyl, or aminoalkyl, straight chained or
 branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl
 or cycloalkenyl.
8. The compound of claim 1, wherein R_9 is H, R_{10} is H, p is 1, and m is 1.

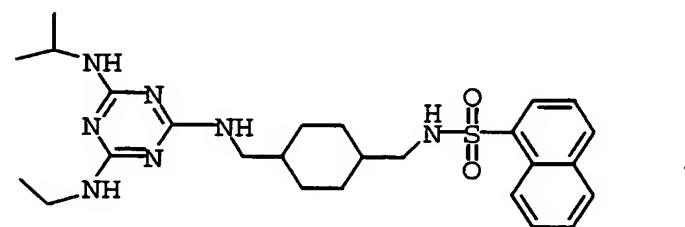
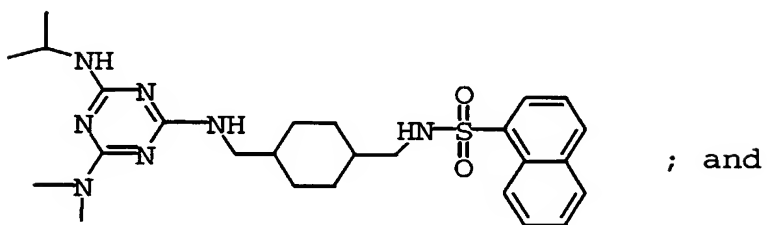
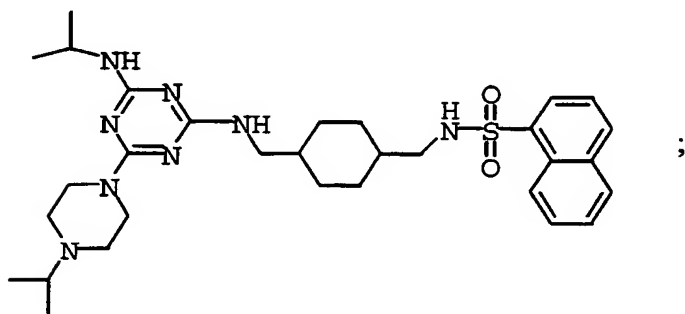
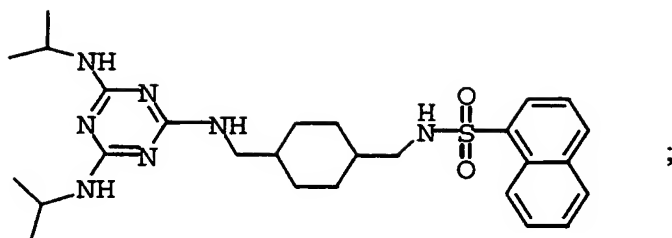
9. The compound of claim 4, wherein R_1 is F, Cl, Br, I, or NR_3R_4 .

10. The compound of claim 9, wherein R_1 and R_2 are both NR_3R_4 where R_3 and R_4 are independently H; straight chained or branched C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or R_3 and R_4 taken together with the nitrogen atom to which they are attached are morpholinyl, piperazinyl, or 1-pyrrolidinyl, wherein the morpholinyl, piperazinyl, or 1-pyrrolidinyl is substituted with one or more straight chained or branched C_1 - C_7 alkyl or C_1 - C_7 phenylalkyl; and wherein the nitrogen atom of the piperazinyl ring is substituted with H; -
 (CH₂)_uYR₅; - (CH₂)_tC(Y)NR₅R₆; - (CH₂)_uNR₅C(Y)R₅; -
 (CH₂)_tC(Y)R₇; - (CH₂)_tCO₂R₅; - (CH₂)_uNR₅R₆; - (CH₂)_uCN; -
 C(Y)R₅; -C(Y)NR₅R₆; -CO₂R₅; straight chained or
 branched C_1 - C_7 alkyl; straight chained or branched C_2 -
 C_7 alkenyl or alkynyl; C_3 - C_7 cycloalkyl or
 cycloalkenyl; phenyl; C_1 - C_6 phenylalkyl; or C_1 - C_6
 heteroarylalkyl.

11. The compound of claim 10, wherein R_{16} is phenyl, 1-naphthyl, quinolinyl, or 2,1,3-benzothiadiazolyl; wherein the phenyl may be substituted with one or more of F, Cl, Br, I, -CN, -NO₂, -NR₅R₆, -
 (CH₂)_nNR₅C(Y)R₅, -SO₂R₅, - (CH₂)_nC(Y)R₇, - (CH₂)_nYR₅,
 - (CH₂)_nC(Y)NR₅R₆, - (CH₂)_nCO₂R₅, - (CH₂)_nSO₂NR₅R₆,
 ethylenedioxy, methylenedioxy, straight chained or
 branched C_1 - C_7 alkyl, monofluoroalkyl,
 polyfluoroalkyl, or aminoalkyl, straight chained or
 branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl
 or cycloalkenyl.

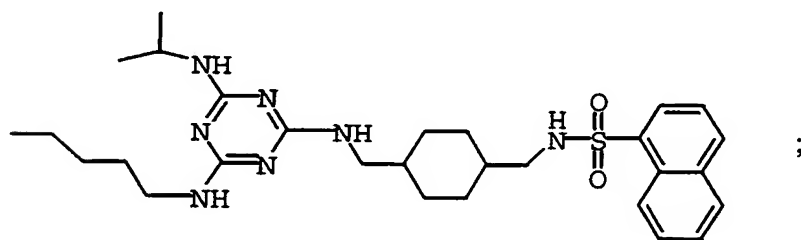
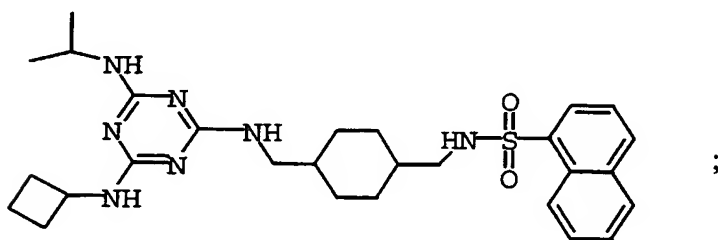
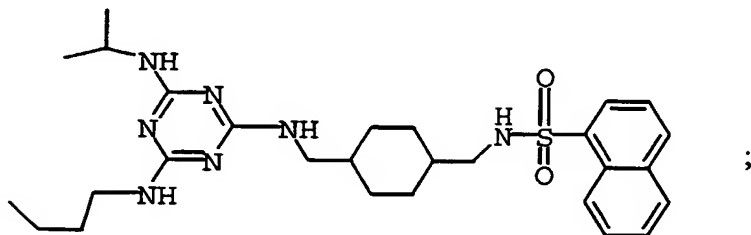
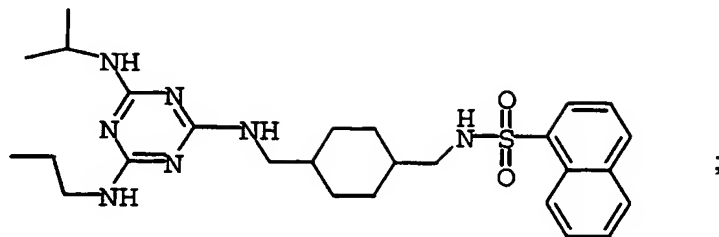
12. The compound of claim 11, wherein R_9 is H, R_{10} is H, p is 1, and m is 1.
- 5 13. The compound of claim 1, selected from the group consisting of:

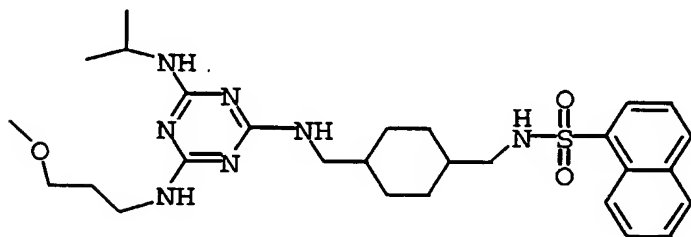
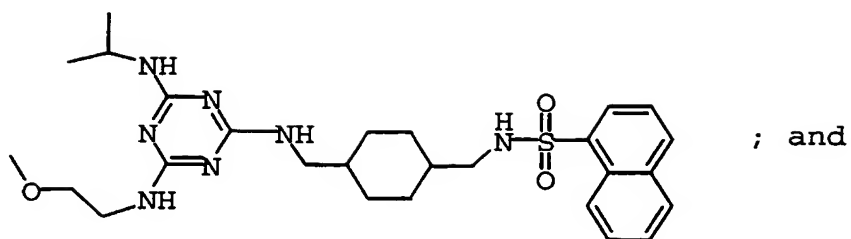




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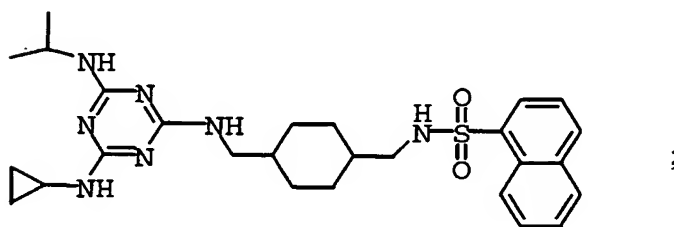
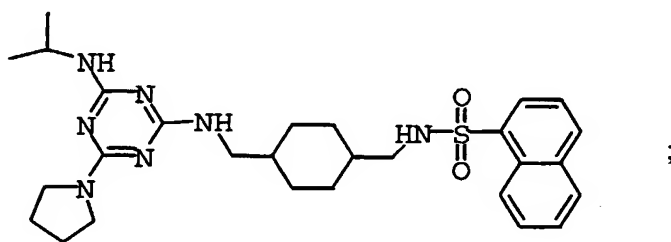
14. The compound of claim 1, selected from the group consisting of:



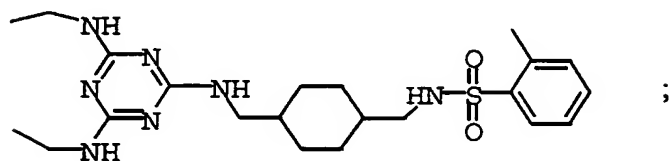
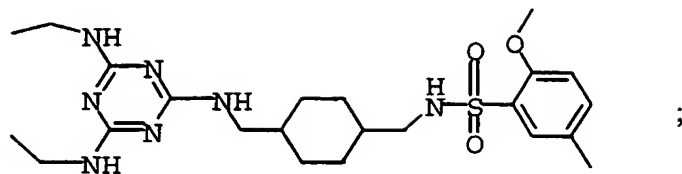


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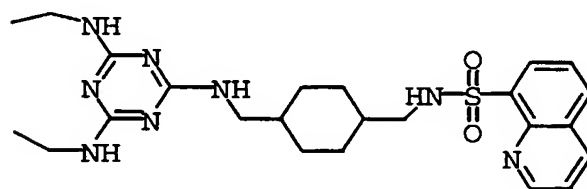
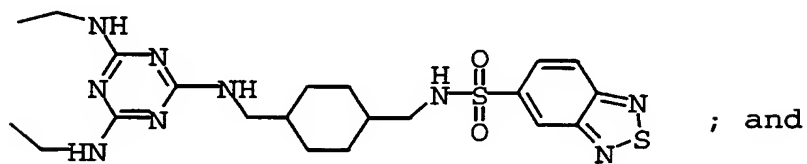
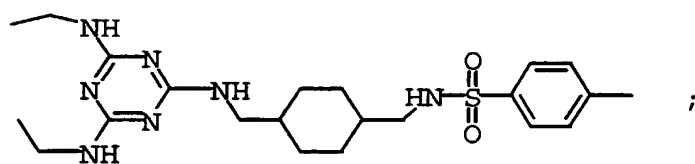
15. The compound of claim 1, selected from the group consisting of:



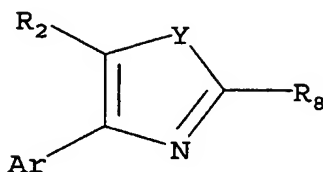
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16. A compound having the structure:



5 wherein Y is O, S or NH;

wherein Ar is a heteroaryl ring that may be optionally substituted with one or more R_1 groups;

10 wherein each R_1 independently is H, F, Cl, Br, -CN, -OH, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, -SO₂C₆H₅, -SO₂NR₅R₆, -C₆H₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, ethylenedioxy, methylenedioxy, perfluoroalkyl, polyfluoroalkyl, aminoalkyl, or straight chained or
15 branched C₁-C₇ alkyl; or phenyl, heteroaryl, or C₁-C₇ phenylalkyl, wherein the phenyl, heteroaryl, or C₁-C₇ phenylalkyl may be substituted with one or more of F, Cl, Br, -CF₃, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, or straight chained or branched C₁-C₄ alkyl;

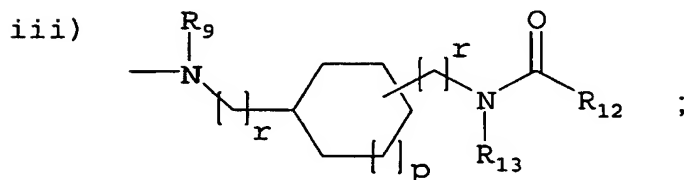
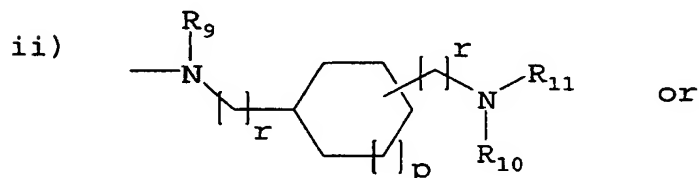
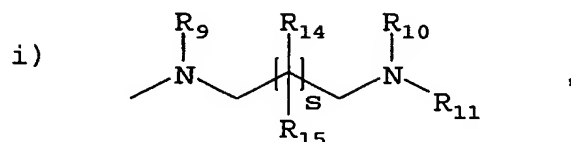
20 wherein R_2 is H, straight chained or branched C₁-C₄ alkyl, -(CH₂)_tOR₅, phenyl optionally substituted with one or more of F, Cl, Br, -CF₃, -CN, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, or straight chained or branched C₁-C₄ alkyl;
25

wherein R_5 is independently H; or straight chained or branched C₁-C₇ alkyl;

wherein R_6 is ²⁵⁴ independently H; or straight chained or branched C_1-C_7 alkyl;

wherein each n independently is an integer from 0 to 6 inclusive;

wherein R_8 is

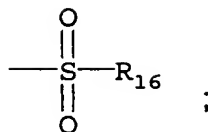


provided that when R_8 is (iii), and Ar is thiazol-2-yl, R_1 cannot be H;

wherein R_9 is independently H; or straight chained or branched C_1-C_4 alkyl;

wherein R_{10} is independently H; or straight chained or branched C_1-C_4 alkyl;

wherein R_{11} is



5 wherein R_{12} is H, straight chained or branched C_1 - C_7 alkyl; or $(\text{CH}_2)_n\text{OR}_{17}$;

 wherein R_{13} is independently $-(\text{CH}_2)_u\text{OR}_5$; -
 $(\text{CH}_2)_t\text{CONR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{NR}_5\text{COR}_5$; $-(\text{CH}_2)_t\text{COR}_7$; -
 10 $(\text{CH}_2)_t\text{CO}_2\text{R}_5$; $-(\text{CH}_2)_u\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{CN}$; straight chained or
 branched C_1 - C_7 alkyl; C_1 - C_7 alkyl in which the C_2 - C_7
 atoms may be optionally substituted with one or more
 F or Cl; C_3 - C_7 cycloalkyl- C_1 - C_7 alkyl; straight chained
 or branched C_2 - C_7 alkenyl; or C_3 - C_5 cycloalkyl;

15 or R_{12} and R_{13} together with the amide linkage to which
 they are attached are pyrrolidinonyl, piperidonyl, or
 oxazolidinonyl;

20 wherein R_7 is independently straight chained or
 branched C_1 - C_7 alkyl;

 wherein R_{14} is H; straight chained or branched C_1 - C_4
 alkyl; F; or $-(\text{CH}_2)_r\text{OR}_5$;

25 wherein R_{15} is H, straight chained or branched C_1 - C_4
 alkyl, or F;

 with the proviso that when R_{14} is -OH, R_{15} cannot be F;

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wherein R_{16} is $-NR_3R_4$, perfluoroalkyl, unsubstituted straight chained or branched C_2-C_7 alkyl, substituted straight chained or branched C_2-C_7 alkyl, wherein the C_2-C_7 alkyl may be substituted with one or more of F, Cl, $-CN$, $-NR_5R_6$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nOCF_3$, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, or C_3-C_7 cycloalkyl; C_3-C_7 cycloalkyl; phenyl, thienyl, isoxazolyl, quinolinyl, or C_1-C_7 phenylalkyl, wherein the phenyl, thienyl, isoxazolyl, quinolinyl, or C_1-C_7 phenylalkyl may be substituted with one or more of F, Cl, Br, I, $-CN$, $-NO_2$, $-NR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight chained or branched C_1-C_3 alkyl, perfluoroalkyl, or aminoalkyl, straight chained or branched C_2-C_7 alkenyl or alkynyl, or C_3-C_7 cycloalkyl or cycloalkenyl; quinolinyl, 1-naphthyl, 2-naphthyl, or 2,1,3-benzothiadiazolyl; wherein the quinolinyl, 1-naphthyl, 2-naphthyl or 2,1,3-benzothiadiazolyl may be substituted with one or more of F, Cl, Br, $-CN$, $-NO_2$, $-NR_5R_6$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, straight chained or branched C_1-C_4 alkyl, perfluoroalkyl, or aminoalkyl;

provided that when R_{16} is quinolinyl and R_8 is (ii), Ar cannot be pyrrolyl;

provided that when R_{16} is $N(CH_3)_2$ and R_8 is (i), Ar cannot be thiazol-2-yl;

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wherein R_3 is independently H; -
 $(CH_2)_uOR_5$; - $(CH_2)_tCONR_5R_6$; - $(CH_2)_uNR_5COR_5$; -
 $(CH_2)_tCOR_7$; - $(CH_2)_tCO_2R_5$; - $(CH_2)_uNR_5R_6$; - $(CH_2)_uCN$;
 straight chained or branched C_1 - C_7 alkyl; straight
 5 chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7
 cycloalkyl or cycloalkenyl; phenyl, or C_1 - C_6
 phenylalkyl; wherein the phenyl, or C_1 - C_6 phenylalkyl
 may be substituted with one or more of F, Cl, Br,
 -CN, -NO₂, -NR₅R₆, -SO₂R₅, - $(CH_2)_nCOR_7$, -
 10 $(CH_2)_nOR_5$, - $(CH_2)_nCONR_5R_6$, - $(CH_2)_nNR_5COR_5$, -
 $(CH_2)_nCO_2R_5$, - $(CH_2)_nSO_2NR_5R_6$, straight chained or
 branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl,
 or aminoalkyl, straight chained or branched C_2 - C_7
 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or
 15 cycloalkenyl;

wherein R_4 is independently H; - $(CH_2)_uOR_5$; -
 $(CH_2)_tCONR_5R_6$; - $(CH_2)_uNR_5COR_5$; - $(CH_2)_tCOR_7$; -
 $(CH_2)_tCO_2R_5$; - $(CH_2)_uNR_5R_6$; - $(CH_2)_uCN$; straight chained or
 20 branched C_1 - C_7 alkyl; straight chained or branched C_2 -
 C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl or
 cycloalkenyl; phenyl or C_1 - C_6 phenylalkyl; wherein the
 phenyl or C_1 - C_6 phenylalkyl may be substituted with
 one or more of F, Cl, Br, -CN, -NO₂, -NR₅R₆,
 25 -SO₂R₅, - $(CH_2)_nCOR_7$, - $(CH_2)_nOR_5$, -
 $(CH_2)_nCONR_5R_6$, - $(CH_2)_nNR_5COR_5$, - $(CH_2)_nCO_2R_5$, -
 $(CH_2)_nSO_2NR_5R_6$, straight chained or branched C_1 - C_7
 alkyl, perfluoroalkyl, polyfluoroalkyl, or
 aminoalkyl, straight chained or branched C_2 - C_7 alkenyl
 30 or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl;

or R_3 and R_4 taken together with the nitrogen atom to
 which they are attached are 1-azetidiny, 1-
 pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl, wherein

the 1-azetidiny, 1-pyrrolidinyl, 1-piperidinyl, or 1H-azepanyl is substituted with one or more of F, -CN, $-(CH_2)_nNR_5R_6$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl, or phenyl or thienyl, or isoxazolyl, or quinolinyl; wherein if $-(CH_2)_nNR_5R_6$, $-(CH_2)_nOR_5$, or $-(CH_2)_nNR_5COR_5$ are in the 2-position, then n is not 0; wherein the phenyl, thienyl, isoxazolyl, or quinolinyl may be substituted with one or more of F, Cl, Br, I, -CN, $-NO_2$, $-NR_5R_6$, $-SO_2R_5$, $-(CH_2)_nCOR_7$, $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-(CH_2)_nCO_2R_5$, $-(CH_2)_nSO_2NR_5R_6$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl;

or R_3 and R_4 taken together with the nitrogen atom to which they are attached are morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl, wherein the morpholinyl, thiomorpholinyl, [1,4]oxazepanyl, [1,4]thiazepanyl, piperazinyl, or [1,4]diazepanyl is optionally substituted with straight chained or branched C_1 - C_5 alkyl or $-(CH_2)_tOR_5$; and wherein the nitrogen atom of the piperazinyl or [1,4]diazepanyl ring may be optionally substituted with $-(CH_2)_uOR_5$; $-COR_5$; straight chained or branched C_1 - C_5 alkyl; or phenyl; wherein the phenyl may be substituted with one or more of F, Cl, Br, -CN, $-NO_2$, $-NR_5R_6$, $-(CH_2)_nOR_5$,

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straight chained or branched C₁-C₃ alkyl,
perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

5 wherein R₁₇ is straight chained or branched C₁-C₄
alkyl, perfluoroalkyl, or polyfluoroalkyl;

wherein each p independently is an integer from 0 to
2 inclusive;

10 wherein each r independently is an integer from 0 to
3 inclusive;

wherein each s independently is an integer from 3 to
6 inclusive;

15 wherein t is an integer from 1 to 4 inclusive;

wherein each u independently is an integer from 2 to
4 inclusive;

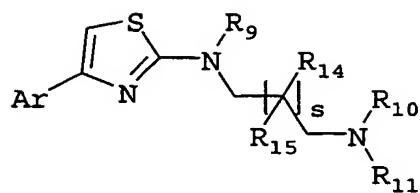
20 or a pharmaceutically acceptable salt thereof.

25 17. The compound of claim 16, wherein the compound
comprises the (+) enantiomer.

18. The compound of claim 16, wherein the compound
comprises the (-) enantiomer.

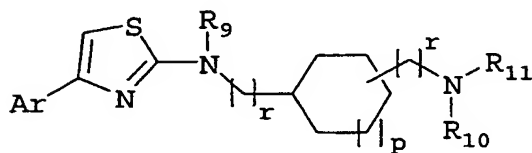
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19. The compound of claim 16 having the structure:



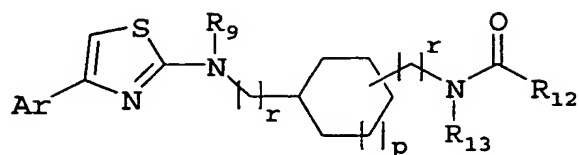
20. The compound of claim 16 having the structure:

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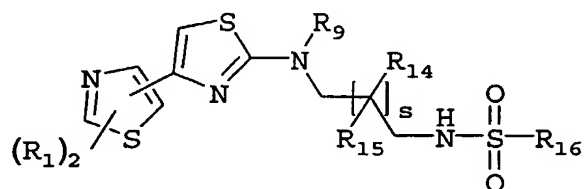
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21. The compound of claim 16 having the structure:



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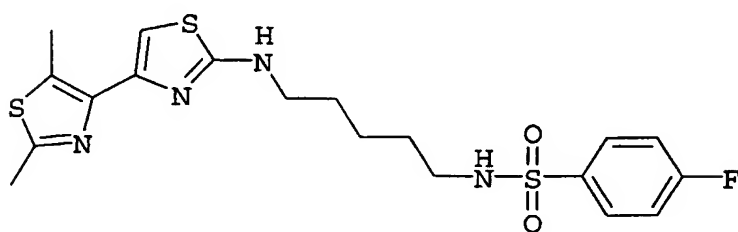
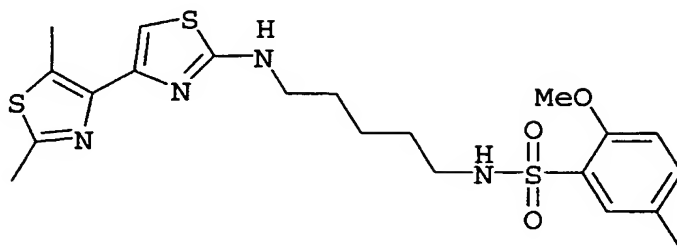
22. The compound of claim 19 having the structure:



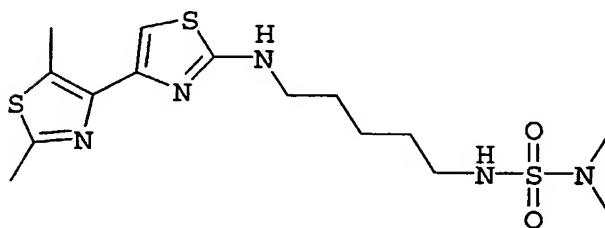
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23. The compound of claim 22 selected from the group consisting of:

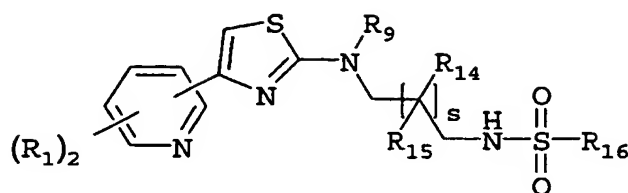


and



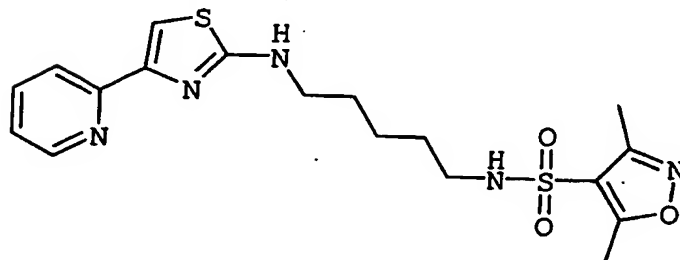
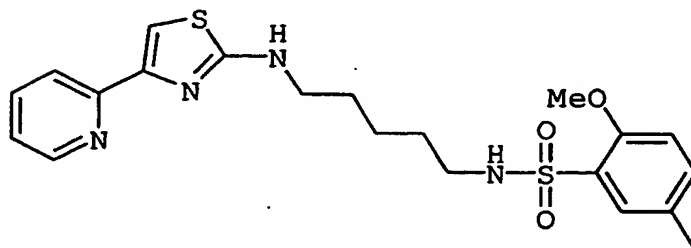
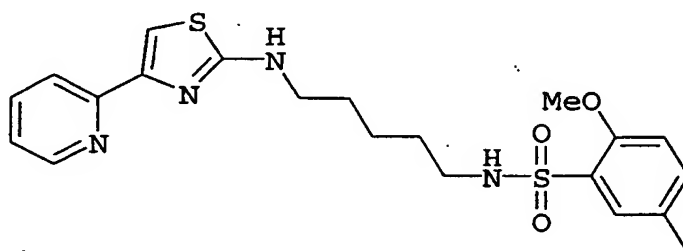
263

24. The compound of claim 19 having the structure:

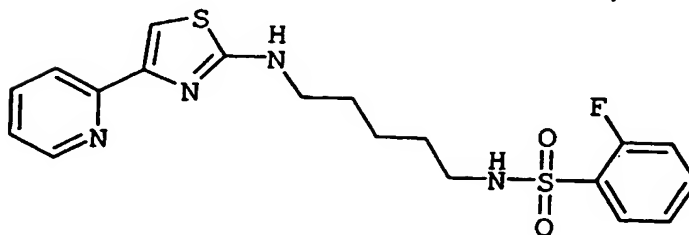
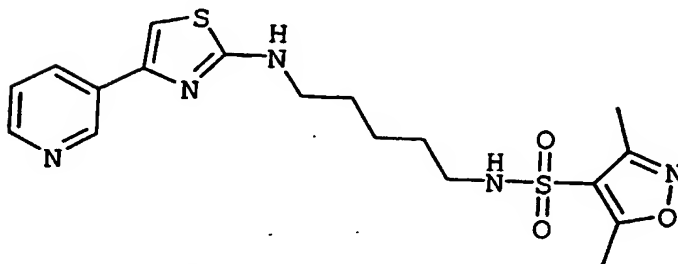


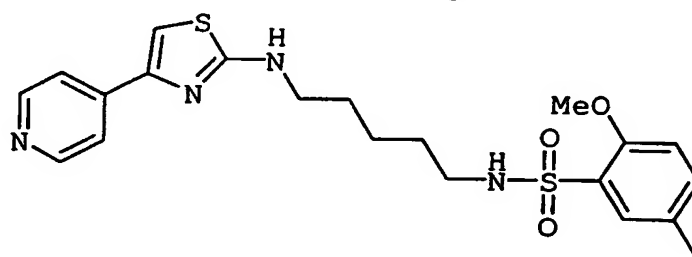
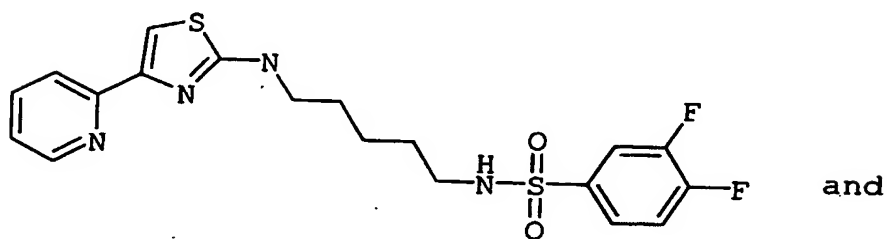
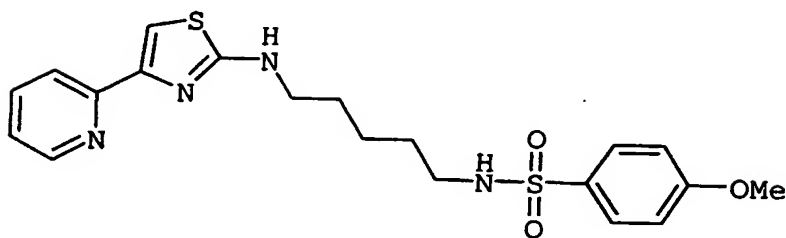
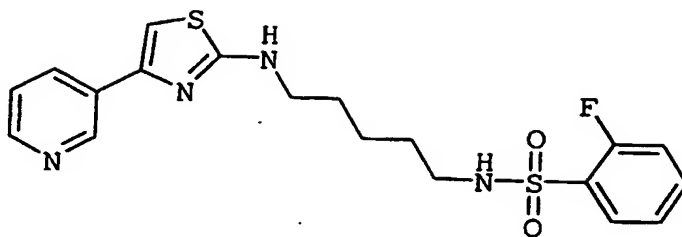
25. The compound of claim 24 selected from the group consisting of:

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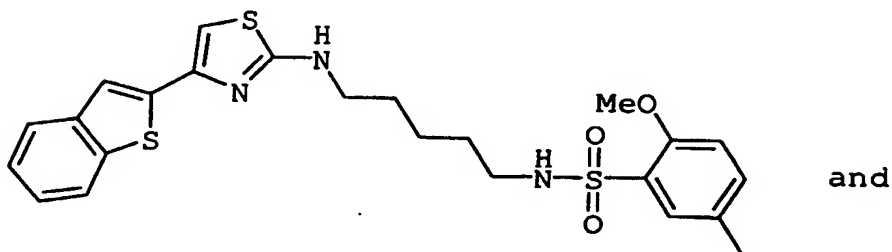
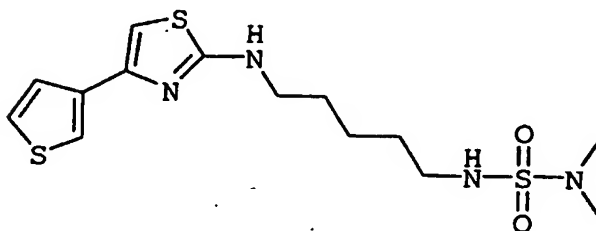
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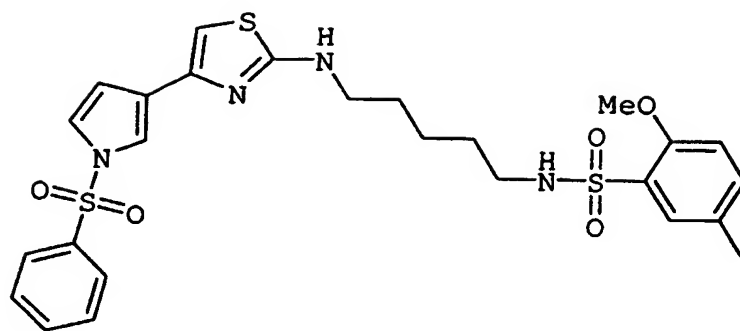


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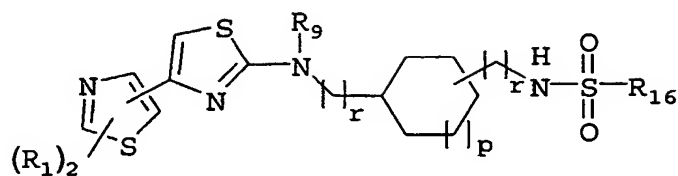
26. The compound of claim 19 selected from the group consisting of:



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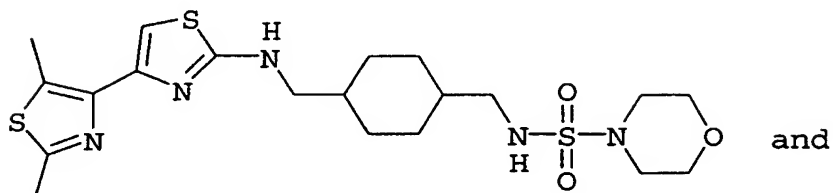
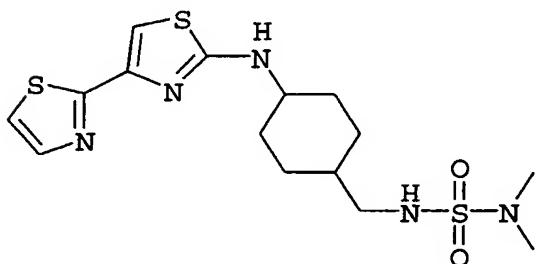
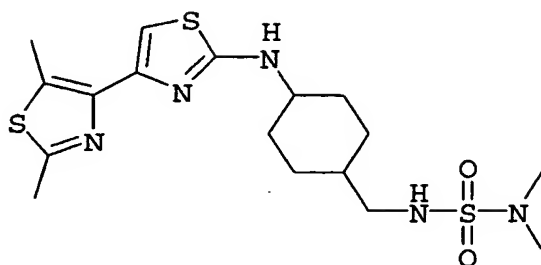


27. The compound of claim 266 having the structure:

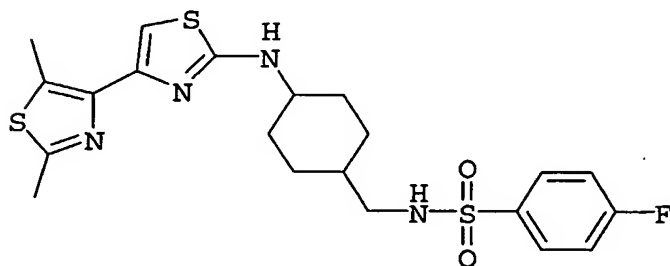


28. The compound of claim 27 selected from the group consisting of:

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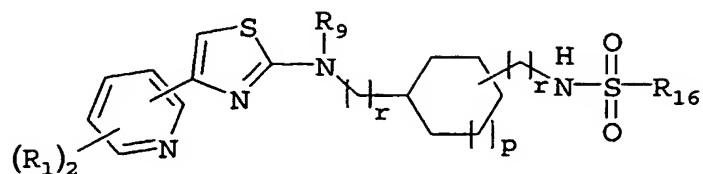


and



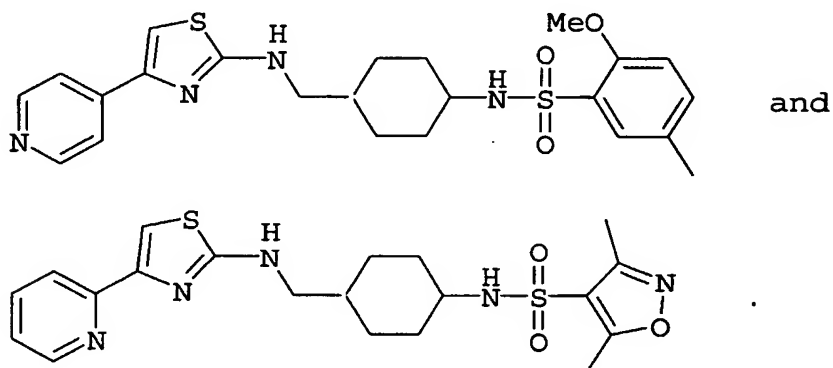
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29. The compound of claim 20 having the structure:



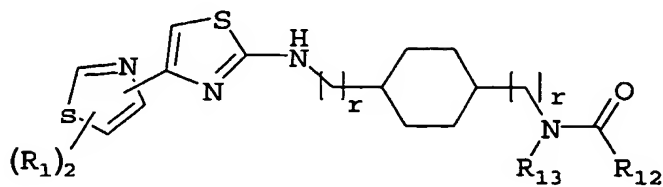
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30. The compound of claim 29 selected from the group consisting of:



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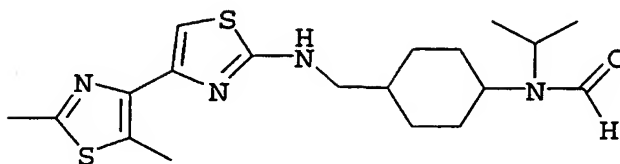
31. The compound of claim 21 having the structure:



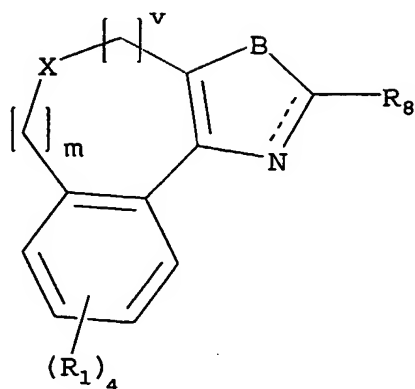
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32. The compound of claim 31, wherein the compound is:



33. A compound having the structure:



5 wherein each R_1 is independently H, F, Cl, Br, -CN, -OH, -NO₂, -NR₅R₆, -SO₂R₅, -(CH₂)_nOR₅, -(CH₂)_nCONR₅R₆, -(CH₂)_nNR₅COR₅, perfluoroalkyl, polyfluoroalkyl, aminoalkyl, or straight chained or branched C₁-C₇ alkyl;

10 wherein R_5 is independently H; or straight chained or branched C₁-C₇ alkyl;

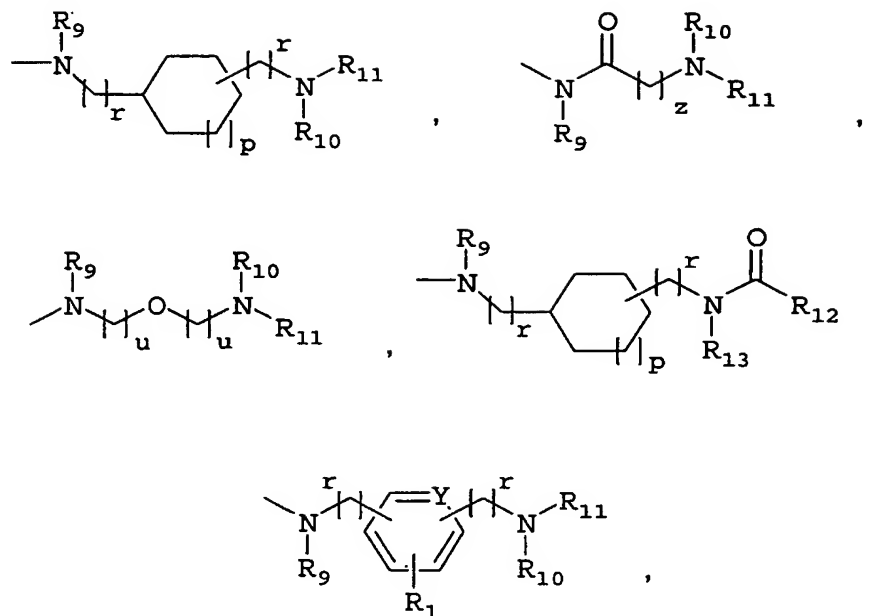
15 wherein R_6 is independently H; or straight chained or branched C₁-C₇ alkyl;

 wherein B is O, NH or S;

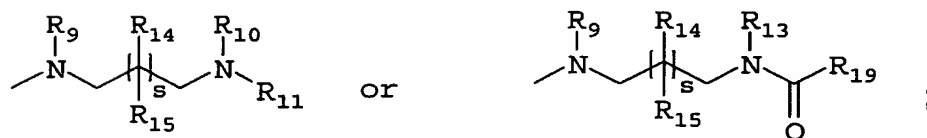
 wherein X is S, SO or SO₂;

20 wherein each n independently is an integer from 0 to 6 inclusive;

wherein R_8 is



5



wherein Y is C or N;

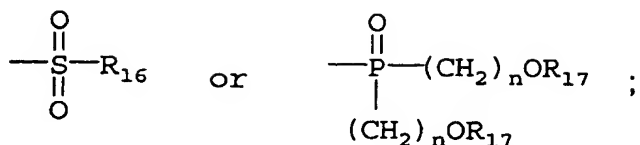
10 wherein R_7 is independently straight chained or branched C_1 - C_7 alkyl;

wherein R_9 is independently H; or straight chained or branched C_1 - C_4 alkyl;

15

wherein R_{10} is independently H; or straight chained or branched C_1 - C_4 alkyl;

wherein R_{11} is



5 wherein R_{12} is H, straight chained or branched C_1 - C_7 alkyl, $(\text{CH}_2)_u\text{OR}_{17}$, or $\text{O}(\text{CH}_2)_u\text{OR}_{17}$; provided that when X is O, R_{12} cannot be methyl;

10 wherein R_{13} is independently H; $-(\text{CH}_2)_u\text{OR}_5$; $-(\text{CH}_2)_t\text{CONR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{NR}_5\text{COR}_5$; $-(\text{CH}_2)_t\text{COR}_7$; $-(\text{CH}_2)_t\text{CO}_2\text{R}_5$; $-(\text{CH}_2)_u\text{NR}_5\text{R}_6$; $-(\text{CH}_2)_u\text{CN}$; straight chained or branched C_1 - C_7 alkyl; C_1 - C_7 alkyl in which the C_2 - C_7 atoms may be optionally substituted with one or more F or Cl; C_3 - C_7 cycloalkyl- C_1 - C_7 alkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; or C_3 - C_7 cycloalkyl; phenyl or C_1 - C_6 phenylalkyl; wherein the phenyl or C_1 - C_6 phenylalkyl may be substituted with one or more of F, Cl, $-\text{CN}$, $-\text{NO}_2$, $-\text{NR}_5\text{R}_6$, $-\text{SO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{COR}_7$, $-(\text{CH}_2)_n\text{OR}_5$, $-(\text{CH}_2)_n\text{CONR}_5\text{R}_6$, $-(\text{CH}_2)_n\text{NR}_5\text{COR}_5$, $-(\text{CH}_2)_n\text{CO}_2\text{R}_5$, $-(\text{CH}_2)_n\text{SO}_2\text{NR}_5\text{R}_6$, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

25 or R_{12} and R_{13} together with the amide linkage to which they are attached are pyrrolidinonyl, piperidonyl, or oxazolidinonyl;

wherein R_{14} is H; straight chained or branched C_1 - C_4 alkyl; F; or $-(\text{CH}_2)_r\text{OR}_5$;

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wherein R_{15} is H, straight chained or branched C_1 - C_4 alkyl, or F;

with the proviso that when R_{14} is -OH, R_{15} cannot be F;

5

wherein R_{16} is perfluoroalkyl, unsubstituted straight chained or branched C_1 - C_7 alkyl, substituted straight chained or branched C_2 - C_7 alkyl, wherein the C_2 - C_7 alkyl may be substituted with one or more of F, Cl, -CN, - SO_2R_5 , - $(CH_2)_nCOR_7$, - $(CH_2)_nOR_5$, - $(CH_2)_nCONR_5R_6$, - $(CH_2)_nNR_5COR_5$, - $(CH_2)_nCO_2R_5$, - $(CH_2)_nOCF_3$, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl; C_3 - C_7 cycloalkyl or cycloalkenyl; phenyl, heteroaryl, or C_1 - C_7 phenylalkyl, wherein the phenyl, heteroaryl, or C_1 - C_7 phenylalkyl may be substituted with one or more of F, Cl, Br, -CN, - NO_2 , - NR_5R_6 , - $(CH_2)_nNR_5COR_5$, - SO_2R_5 , - $(CH_2)_nCOR_7$, - $(CH_2)_nOR_5$, - $(CH_2)_nCONR_5R_6$, - $(CH_2)_nCO_2R_5$, - $(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl, straight chained or branched C_2 - C_7 alkenyl or alkynyl, or C_3 - C_7 cycloalkyl or cycloalkenyl; quinolinyl, 1-naphthyl, 2-naphthyl, or 2,1,3-benzothiadiazolyl; wherein the quinolinyl, 1-naphthyl, 2-naphthyl or 2,1,3-benzothiadiazolyl may be substituted with one or more of F, Cl, Br, -CN, - NO_2 , - NR_5R_6 , - $(CH_2)_nNR_5COR_5$, - SO_2R_5 , - $(CH_2)_nCOR_7$, - $(CH_2)_nOR_5$, - $(CH_2)_nCONR_5R_6$, - $(CH_2)_nCO_2R_5$, - $(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy, straight chained or branched C_1 - C_7 alkyl, perfluoroalkyl, polyfluoroalkyl, or aminoalkyl;

30

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with the proviso that when R_8 is $NR_9(R_{14}R_{15})_sNR_{10}R_{11}$, R_{16} cannot be quinolinyl;

5 wherein R_{17} is H, straight chained or branched C_1 - C_4 alkyl, perfluoroalkyl, or polyfluoroalkyl;

10 wherein R_{19} is $-(CH_2)_uOR_5$, $-NR_5R_6$, phenyl, or heteroaryl, wherein the phenyl or heteroaryl may be substituted with one or more of F, Cl, Br, -CN, -
15 NO_2 , $-NR_5R_6$, $-(CH_2)_nNR_5COR_5$, $-SO_2R_5$, $-(CH_2)_nCOR_7$,
 $-(CH_2)_nOR_5$, $-(CH_2)_nCONR_5R_6$, $-(CH_2)_nCO_2R_5$,
 $(CH_2)_nSO_2NR_5R_6$, ethylenedioxy, methylenedioxy,
straight chained or branched C_1 - C_7 alkyl,
perfluoroalkyl, polyfluoroalkyl, or aminoalkyl,
20 straight chained or branched C_2 - C_7 alkenyl or alkynyl,
or C_3 - C_7 cycloalkyl or cycloalkenyl;

wherein m is 0 or 1;

20 wherein each p independently is an integer from 0 to 2 inclusive;

wherein each r independently is an integer from 0 to 3 inclusive;

25 wherein each s independently is an integer from 1 to 6 inclusive;

wherein t is an integer from 1 to 4 inclusive;

30 wherein each u independently is an integer from 2 to 4 inclusive;

wherein v is 1 or 2;

with the proviso that when v is 2, m is 0;

wherein z is an integer from 2 to 7;

5

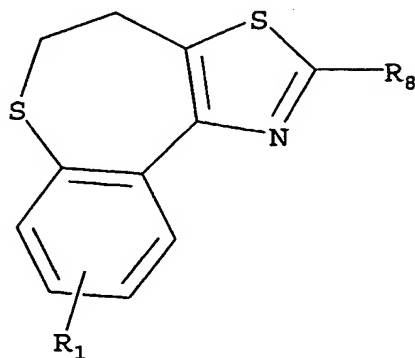
or a pharmaceutically acceptable salt thereof.

10

34. The compound of claim 33, wherein the compound comprises the (+) enantiomer.

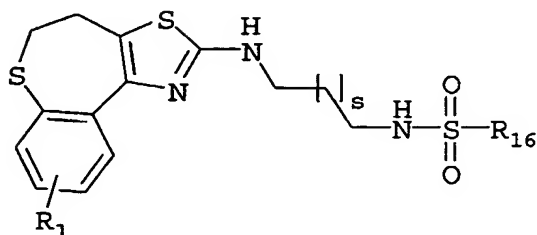
35. The compound of claim 33, wherein the compound comprises the (-) enantiomer.

36. The compound of claim ²⁷⁶ 33 having the structure:



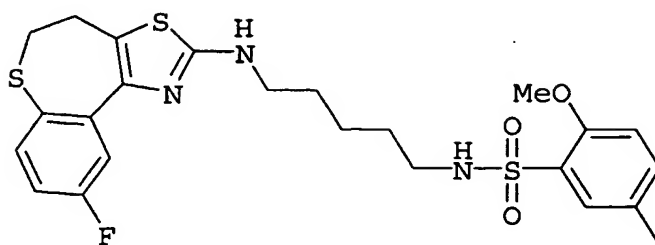
5

37. The compound of claim 36 having the structure:

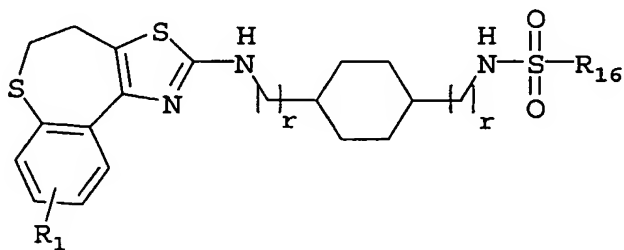


10

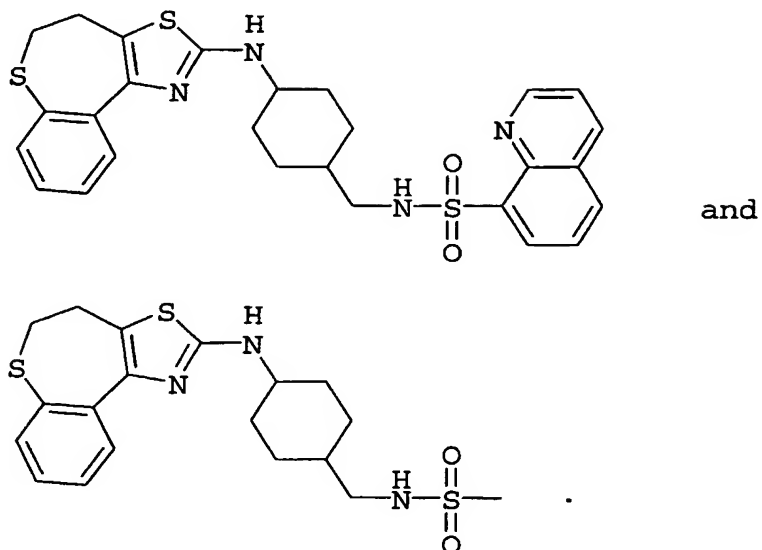
38. The compound of claim 37 having the structure:



5 39. The compound of claim 36 having the structure:

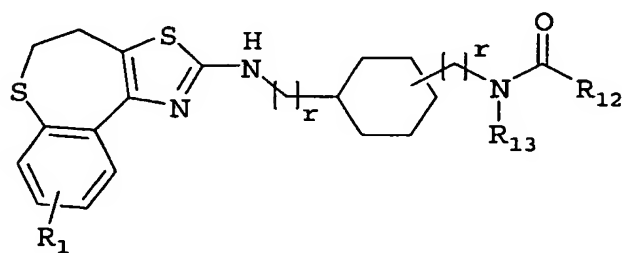


40. The compound of claim 39 selected from the group consisting of:



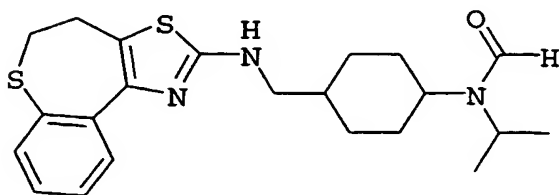
5

41. The compound of claim 36 having the structure:



10

42. The compound of claim 41 having the structure:



43. A pharmaceutical composition comprising a
therapeutically effective amount of the compound of
claim 1, 16, or 33 and a pharmaceutically acceptable
carrier.

44. A pharmaceutical composition of claim 43, wherein the
amount of the compound is an amount from about 0.01
mg to about 800 mg.

45. A pharmaceutical composition of claim 44, wherein the
amount of the compound is an amount from about 0.01
mg to about 500 mg.

46. A pharmaceutical composition of claim 45, wherein the
amount of the compound is an amount from about 0.01
mg to about 250 mg.

47. A pharmaceutical composition of claim 46, wherein the
amount of the compound is an amount from about 0.1 mg
to about 60 mg.

48. A pharmaceutical composition of claim 47, wherein the
amount of the compound is an amount from about 1 mg
to about 20 mg.

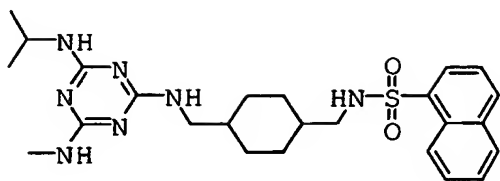
49. The pharmaceutical composition of claim 43, wherein
the carrier is a liquid and the composition is a
solution.

50. The pharmaceutical composition of claim 43, wherein
the carrier is a solid and the composition is a
tablet.

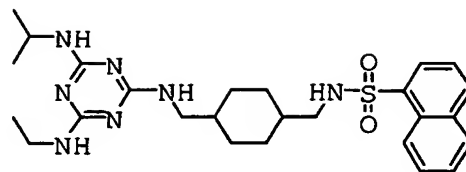
51. The pharmaceutical composition of claim 43, wherein the carrier is a gel and the composition is a suppository.
- 5 52. A pharmaceutical composition made by combining a therapeutically effective amount of the compound of claim 1, 16, or 33 and a pharmaceutically acceptable carrier.
- 10 53. A process for making a pharmaceutical composition comprising combining a therapeutically effective amount of the compound of claim 1, 16, or 33 and a pharmaceutically acceptable carrier.
- 15 54. Use of the chemical compound of claim 1, 16, or 33 for the preparation of a pharmaceutical composition for treating an abnormality, wherein the abnormality is alleviated by decreasing the activity of a human Y5 receptor.
- 20 55. Use of the compound of claim 54, wherein the abnormality is an eating disorder, obesity, bulimia nervosa, a sexual disorder, a reproductive disorder, depression, an epileptic seizure, hypertension, cerebral hemorrhage, congestive heart failure, or a sleep disturbance.
- 25

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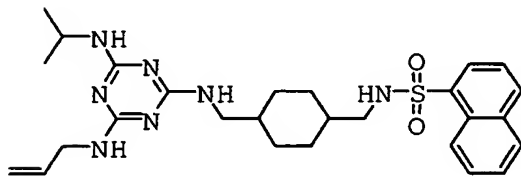
FIGURE 1A



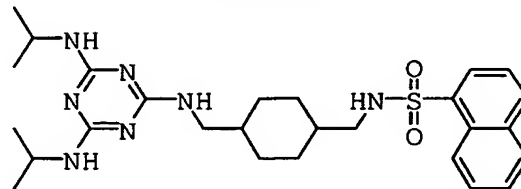
Example 1



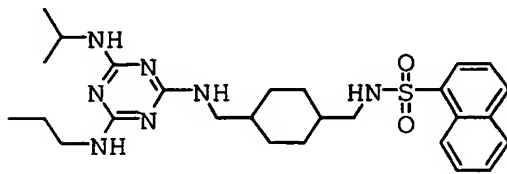
Example 2



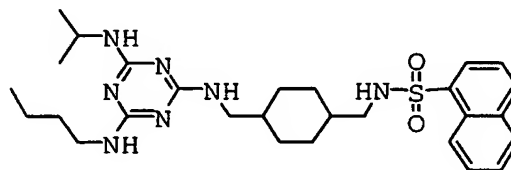
Example 3



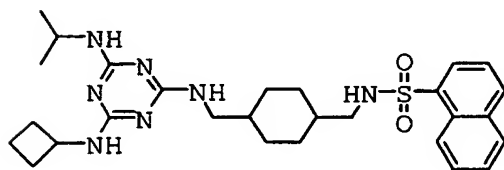
Example 4



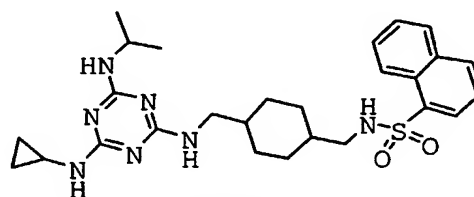
Example 5



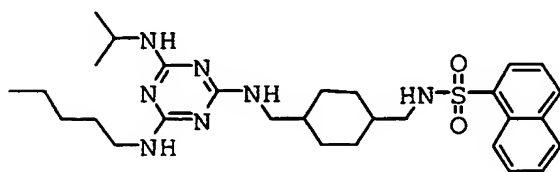
Example 6



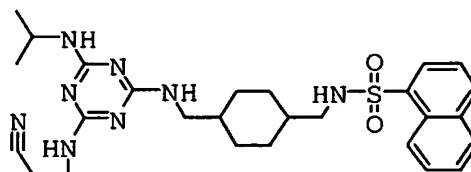
Example 7



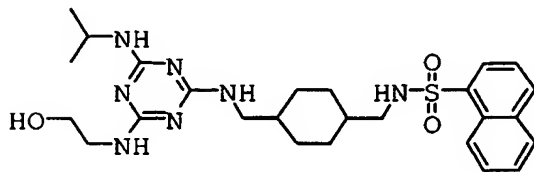
Example 8



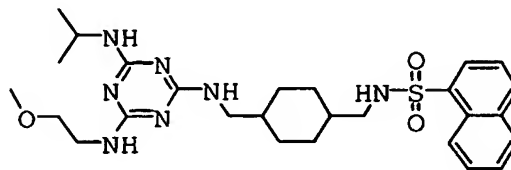
Example 9



Example 10



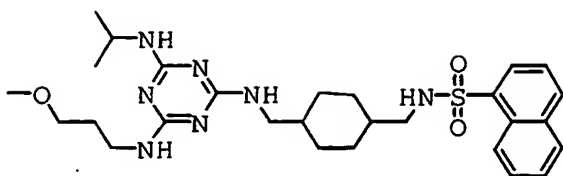
Example 11



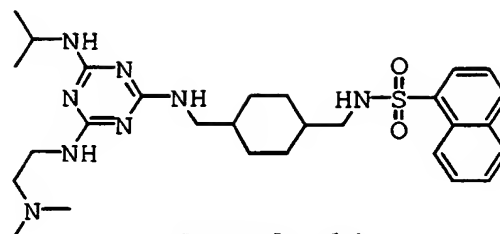
Example 12

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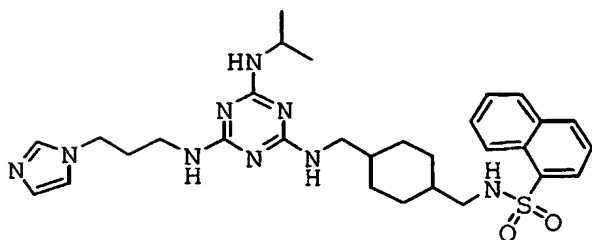
FIGURE 1B



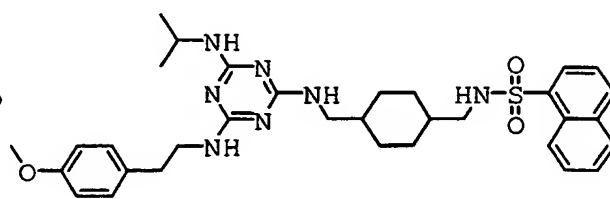
Example 13



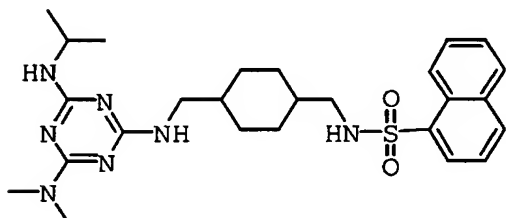
Example 14



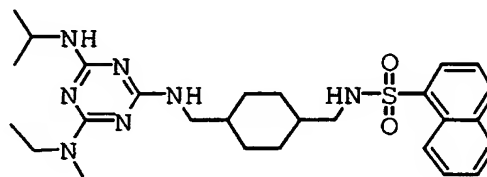
Example 15



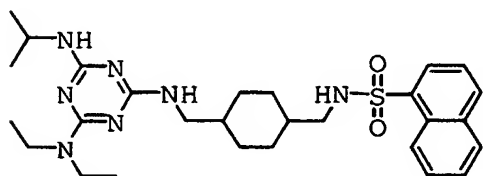
Example 16



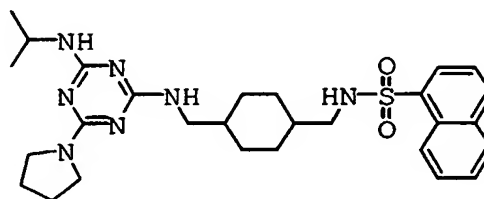
Example 17



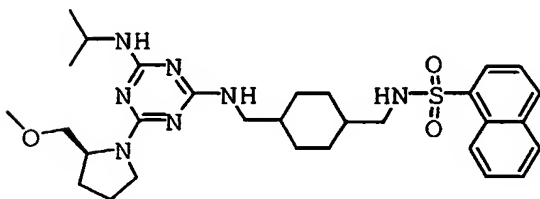
Example 18



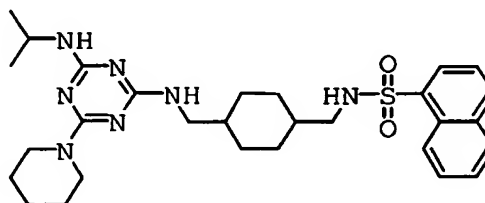
Example 19



Example 20



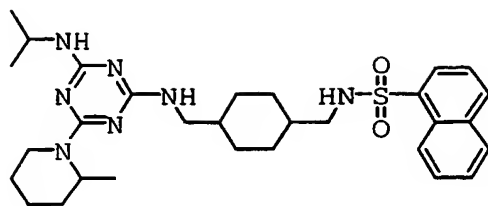
Example 21



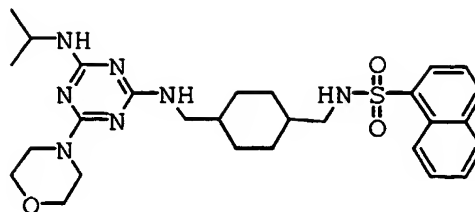
Example 22

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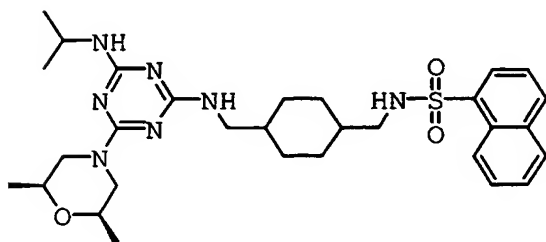
FIGURE 1C



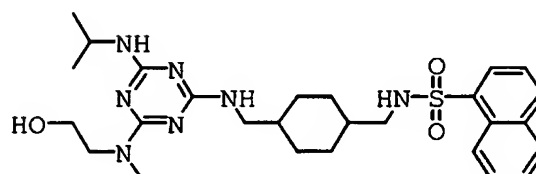
Example 23



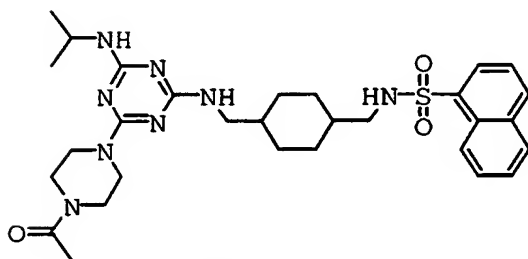
Example 24



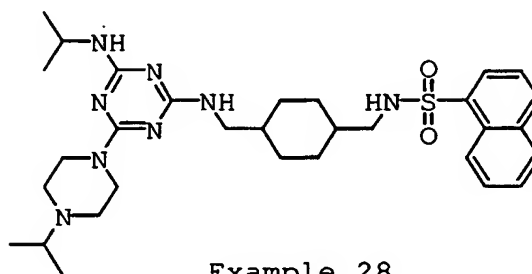
Example 25



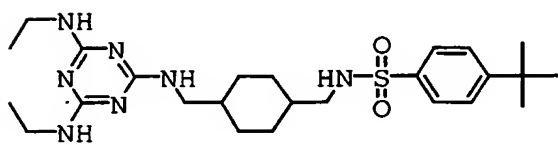
Example 26



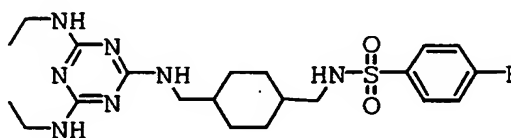
Example 27



Example 28



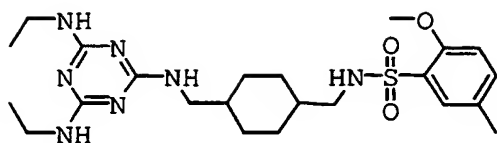
Example 29



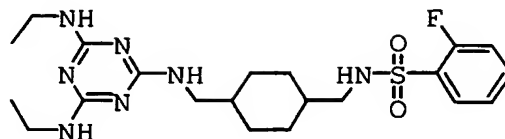
Example 30

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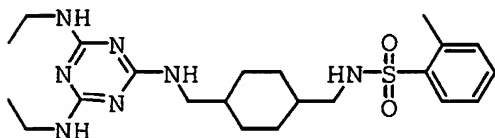
FIGURE 1D



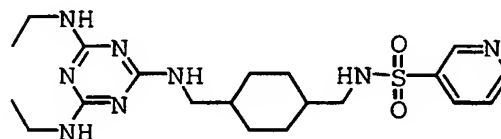
Example 31



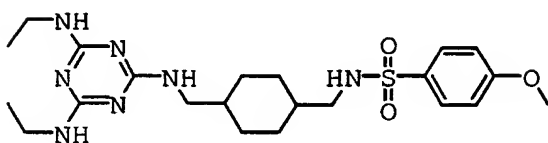
Example 32



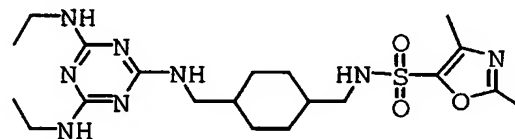
Example 33



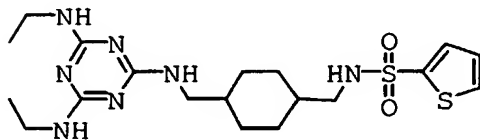
Example 34



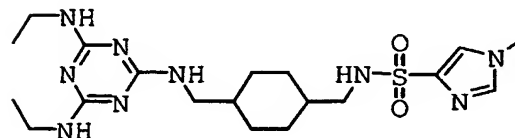
Example 35



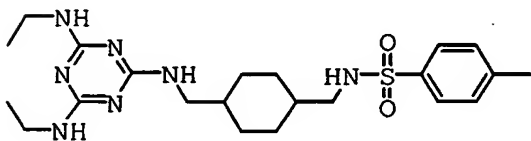
Example 36



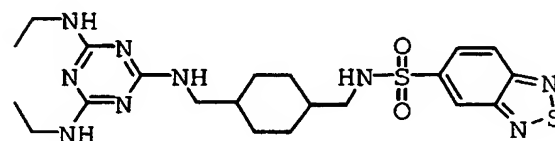
Example 37



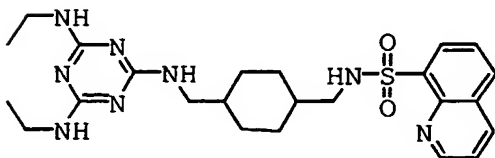
Example 38



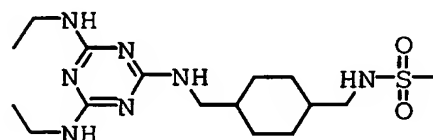
Example 39



Example 40



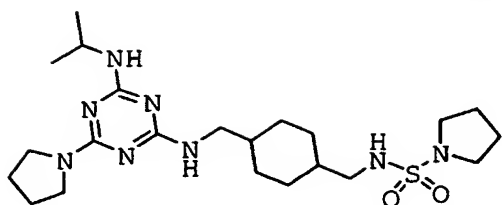
Example 41



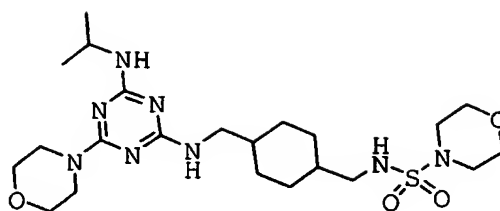
Example 42

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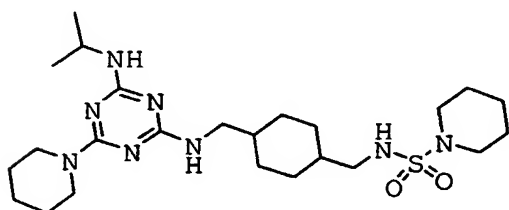
FIGURE 1E



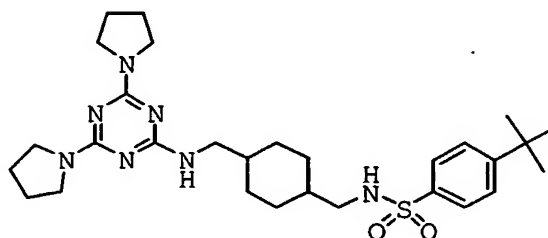
Example 43



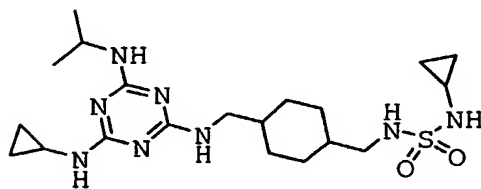
Example 44



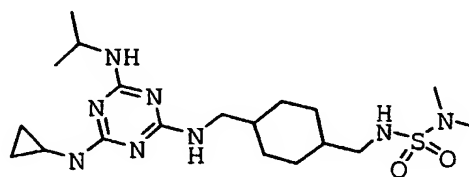
Example 45



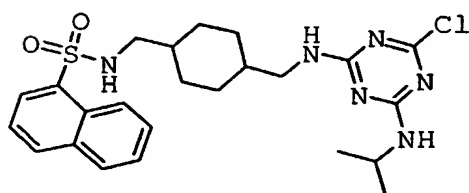
Example 46



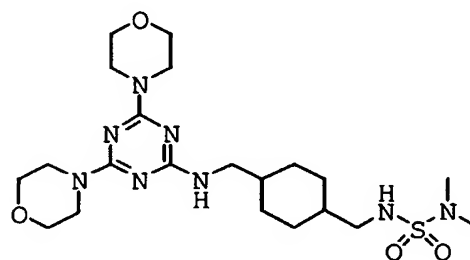
Example 47



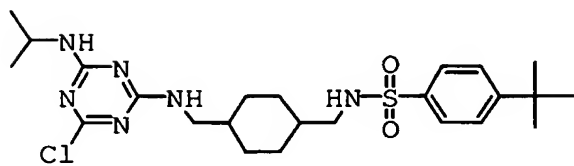
Example 48



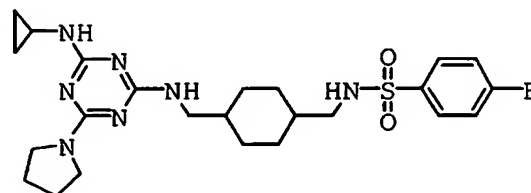
Example 49



Example 50



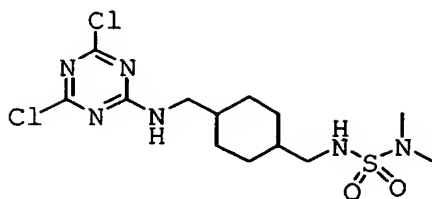
Example 51



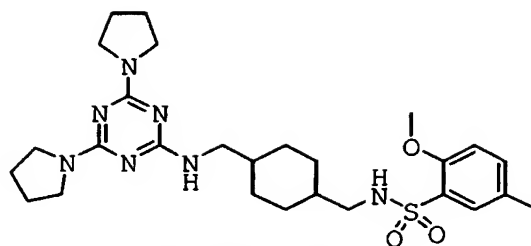
Example 52

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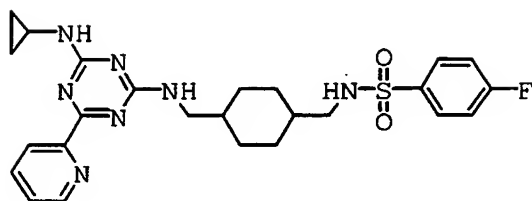
FIGURE 1F



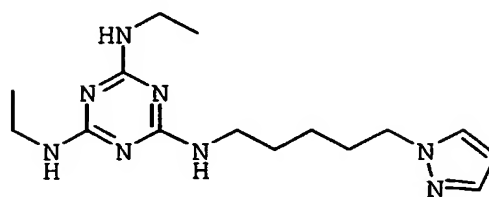
Example 53



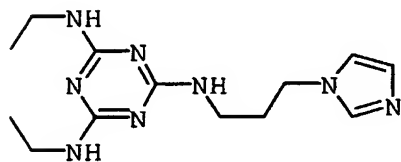
Example 54



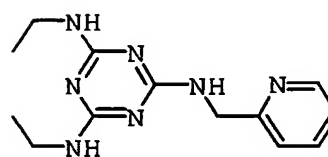
Example 55



Example 56



Example 57



Example 58

INTERNATIONAL SEARCH REPORT

International application N .

PCT/US00/10784

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C07D 251/70, 277/28, 513/04; A61K 31/427, 31/429, 31/53; A61P 3/04; 7/04, 9/12.

US CL : 544/198, 209; 548/151, 190, 193, 194; 514/245, 366.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/198, 209; 548/151, 190, 193, 194; 514/245, 366.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 05138 A1(ZENYAKU KOGYO KABUSHIKI KAISHA) 04 February 1999(04.02.1999), see entire document, especially page 12-14.	1-12 and 43-53
X	EP 0 775 487 A1(NIPPON SHINYAKU COMPAN7, LIMITED.) 28 May 1997(28.05.1997) , see entire document especially page s3-4 and pages 6-24.	1-12 and 43-53
X	US 5,536,722 A (COE et al.) 16 July 1996 (16.07.1996), see col. 2-5 and col. 7-16	1-12 and 43-53
X	US 5,238,936 A (REGNIER et al.) 24 August 1993 (24.08.1993), see col. 2-5 and col. 7-16.	1-12 and 43-53
X	XIA et al. Substituted 1,3,5-Triazines As Cholesteryl Ester Transfer Protein Inhibitors. Bioorg. Med. Chem. Lett. 1996, Vol. 6, No. 7, pages 919-922, especially see page 919-920	1-12 and 43-53
A	US 5,232,921 A (BIZIERE et al.) 03 August 1993 (03.08.1993), see entire document.	16-32 and 43-53



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

05 July 2000 (05.07.2000)

Date of mailing of the international search report

28 JUL 2000

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile N . (703)305-3230

Authorized officer

Venkataraman Balasubramanian

Telephone No. (703)308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/10784

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 1-32 and 33-55 (in part)
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/10784

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

- I. Claims 1-15 and 43-55 drawn to triazine compounds and pharmaceutical composition where the core ring is triazine
- II. Claims 16-32 and 43-55 drawn to compound of claim 16 and pharmaceutical composition where Y = S.
- III. Claims 16 and 43-55 drawn to compound of claim 16 and pharmaceutical composition where Y = O.
- IV. Claims 16 and 43-55 drawn to compound of claim 16 and pharmaceutical composition where Y = NH.
- V. Claims 33-55 drawn to compound of claim 33 and pharmaceutical composition where B = S.
- VI. Claims 33, 43-55 drawn to compound of claim 33 and pharmaceutical composition where B = O.
- VII. Claims 33, 43-55 drawn to compound of claim 33 and pharmaceutical composition where B = NH.

The inventions listed as Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Groups I-VII relate to structurally dissimilar compounds that lack common core namely triazine vs. thiazole vs. oxazole vs. imidazole vs. tricyclic thiazole vs tricyclic oxazole vs tricyclic imidazole which are not art recognized equivalent of each other.

The sole feature common to the groups which does not vary is a ring with at least one nitrogen which by itself cannot be considered to define a novel contribution over prior art given such fragment with substituents is known in the prior art and therefore would not constitute a special technical feature as defined by PCT Rule 13.2.